"A STUDY ON 100 CASES OF KERATOMYCOSES TO COMPARE THE EFFICACY OF TOPICAL 10% SODIUM CHLORIDE WITH 5% NATAMYCIN VERSUS 5% NATAMYCIN ALONE AS A TREATMENT STRATEGY"

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CERTIFICATE

This is to certify that this dissertation titled **"A STUDY ON 100 CASES OF KERATOMYCOSES TO COMPARE THE EFFICACY OF TOPICAL 10% SODIUM CHLORIDE WITH 5% NATAMYCIN VERSUS 5% NATAMYCIN ALONE AS A TREATMENT STRATEGY"** is a bonafide work done by Dr.K.RAVIKUMAR, M.S post graduate in ophthalmology, at Regional Institute of ophthalmology and Government Ophthalmic Hospital, Egmore, Chennai - 600008, attached to Madras Medical College, during the academic year 2003 – 2006.

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PART-1

INTRODUCTION

Keratomycosis is extremely common in tropics and is an important cause of corneal morbidity. Fungi are opportunistic agents infecting the cornea.Seldom they infect healthy cornea; Most often there exists some predisposing factor which help colonization of fungi.[Forster,R.K Rebell,G.The diagnosis and management of keratomycoses. Arch.ophthalmol.93:975,1975].

Fungal infections of the cornea remain a therapeutic challenge to ophthalmologists even today due to interplay of various factors like delayed presentation, chronicity of the infection, resistance to antifungal agents, resemblance to other forms of stromal keratitis and superadded bacterial infections. More than 68 species of fungi are known to cause keratomycosis globally.

Early recognition and treatment is crucial in containing the disease which is why, various newer modalities of treatment are being constantly worked.

In our study, we worked on 100 cases of fungal keratitis and have established topical 10% Sodium chloride as a useful adjunct in the management of keratomycosis.

EPIDEMIOLOGY

Fungal spores are ubiquitous, produced in large numbers and are highly resistant. They germinate and subsist on organic substrates.

Fungi causing keratomycosis by and large belong to moniliaceae, Dematiaceae and yeast like Candida.

Moniliaceae include light coloured fungi like Fusarium and Aspergillus Species while Dematiaceae include dark coloured fungi like Alternaria and Curvularia.

In South India, Aspergillus is the common causative fungus (36%) in keratomycosis followed by Penicillium species (29%). Fusarium keratomycosis is not as common as reported in the literature. In endophthalmitis there is a preponderance of Penicillium as the causative fungus.

Mycotic endophthalmitis is seen following cataract surgery in 64% of cases.

Contrary to expectations, onset of endophthalmitis often occurs within 2 weeks of surgery in most cases.

Trauma with organic matter is an important predisposing factor in keratomycosis. These observations are discussed in relation to the clinical features.

[R.Srinivasan, Kanungo.R, Goyal J.L, Spectrum of oculomycosis in south India. Acta. ophthalmol 1991;]

Candida and Aspergillus are more common in cooler climates.

FUSARIUM:

Fusarium species are saprophytic fungi which grow on decaying vegetation and on wild and cultivated plants. Agricultural labourers are predisposed to infections by this organism. F.solani is the most common culprit.

CANDIDA:

Keratomycosis due to Yeast is most commonly due to C.albicans.

C.parapsilosis is a rare isolate.

ASPERGILLUS:

Aspergillus thrives on corn, soil and decaying vegetation.

Hospital air has abundant spores.

Aspergillus has been isolated from both tropical and temperate zones.

A.fumigatus is the most common isolate although A.flavus and

A.niger has also been reported.

GENERAL MYCOLOGY

Fungi are eukaryotic protists that differ from bacteria and other prokaryotes.They have rigid cell walls containing chitin, mannan and other polysaccharides.Cytoplasmic membrane contains sterols.

They possess true nuclei with nuclear membrane and paired chromosomes.

They divide sexually, asexually or either way. They may be unicellular or bicellular.

Hypha is a thread like, tubular structure produced by cell elongation. Mycelia are a tangled mass of hyphae. Moulds or filamentous fungi form mycelia.

Mycelia can be vegetative mycelia which grows into the media or aerial mycelia which projects from the surface.

MORPHOLOGY

FUSARIUM:

They have characteristic microconidia and macroconidia.The main identifying feature is the large banana shaped macroconidia that are produced on short lateral hyphae. Fusarium produces macroconidia on sporodochia. This sporodochial type mutates forming a mycelial type, with abundant aerial mycelia and a pionnotal type, which produces lots of conidiophores in sheets across the culture. Macroconidia are septate with apical and basal cells.

ASPERGILLUS:

Aspergillus is easy to identify morphologically by the Conidiophore with its swollen end surrounded by flask shaped sterigmata, each of which produces long chains of coccoid conidia that radiate from the terminal end. Hyphae are septate and branch dichotomously .

Rapidly progressing infections have regular hyphae while indolent lesions have irregular hyphae.

DEMATIACIOUS FUNGI:

These fungi produce brown pigmentation of colonies and are saprophytic.

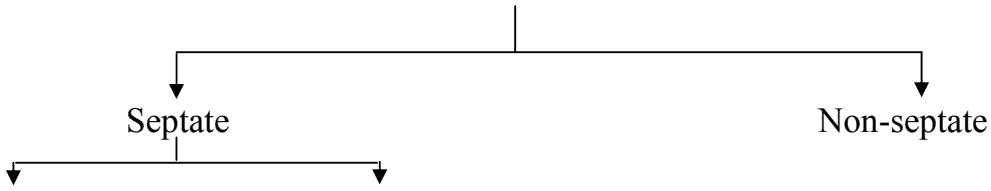
CANDIDA:

They are ovoid or spherical budding yeasts; Base of the bud is narrow, and the bud is slightly off axis. They lack symmetry. Both true and pseudo hyphae are seen of which the mycelial form is the invasive form.

Presence of hyphal elements in addition to yeast forms in Gram stained specimens is indicative of tissue colonization. Candida albicans produces characteristic chlamydospores.

CLASSIFICATION OF FUNGI

1.Moulds



Pigmented	Non-pigmented	Rhizopus
		Absida
Alternaria	Aspergillus	Mucor
Curvularia	Acremonium	
Cladosporium	Cylindrocarpon	
Drechslera	Fusarium	
Melanconiales	Myrathecum	
Sphaeropsidales	Allescheria boydii	
	Penicillium	
	Volutella	

2. Dimorphic Fungi

Blastomyces
Sporothrix
Coccidioides
Histoplasma

3. Yeasts

Candida
Cryptococcus
Rhodotorulae

CULTURAL CHARACTERISTICS

Sabouraud's dextrose agar without cycloheximide and Brain Heart Infusion broth with chloramphenicol are the preferred media for isolation of corneal pathogens.

Media should be incubated for a minimum of two weeks and ideally one month. Fungal isolation is usually performed at room temperature [25 degrees Celsius]. One set of culture media is incubated at 37 degrees Celsius for thermophylic fungi. Agar plates are placed in a plastic bag containing moisture pack to enhance its life.

Majority of fungi causing keratitis can be identified in culture within 3 days. Aspergillus and Fusarium colonies appear within 48 hours in blood agar, Sabouraud's dextrose agar and Brain Heart Infusion agar. However appreciable colonies appear only after 1-2 weeks. Media should be observed for at least 2 weeks before they are considered negative.

Growth rate,colony characteristics, pigmentation,microscopic appearance are considered for species identification.

PATHOGENESIS

Fungal keratitis is more prevalent in warmer climates.In south India prevalence is more in September and October during harvest. Any persistent epithelial defect, prolonged topical steroids, trivial injuries, Herpes simplex infection, contact lens wear, predispose eyes to fungal infection.

Most of the keratomycosis is due to saprophytic fungi present in lids and conjunctiva, like candida, Aspergillus,Penicillium, Rhodotorula, Cladosporium and Alternaria.

Damage to cornea is often secondary to,

a) Disruption of corneal lamellae by direct invasion of fungal hyphae,

b) Inflammatory response elicited by the attendant T-cells, polymorphonuclear leucocytes and

c)Tissue destruction caused by fungal toxins.

Fungal keratitis often resembles other forms of stromal keratitis and escapes clinical attention for quite long time before presentation.

Incubation period varies from 2 days to 2 weeks allowing extensive invasion by fungal filaments.

Histopathological examination often reveals presence of mycelia parallel to corneal lamellae .

Perpendicular orientation of hyphae indicates virulent fungi. [Naumann,Green,Zimmerman et.al A Histopathological study of 73 cases of mycobial keratitis American journal of ophthalmology 1967].

Candida albicans, especially the yeast forms with surface mannoprotein adhesions can cause keratomycosis.

Increased virulence is often attributed to the ability to form hyphae. This is due to the greater potential of these hyphal forms to get attached to corneal surface.

Also mannoproteins found on hyphal and pseudo hyphal forms inhibit neutrophil chemotaxis and subsequent phagocytosis by these cells. [Nelson R.D et.al,candida mannan;chemistry,suppression of cell mediated immunity & possible mechanisms of action ;clinical microbiological review, 1991]. Leucocyte infiltration of cornea adds to further insult in fungal keratitis.

Ring abscesses demonstrate neutrophils, while plasma cells and occasional eosinophils around fungal filaments are not uncommon. Size of fungal filaments pose a problem for neutrophil phagocytosis.But still neutrophils exert their fungicidal effect by release of lysosomal enzymes and oxygen metabolites.Associated tissue destruction is almost inevitable. Fungi produce cytotoxins and toxic enzymes.

Cytotoxins include,

Aflatoxins and ochrotoxins [Aspergillus]

Trichothenes [Fusarium and Acremonium]

Gliotoxins [Aspergillus,penicillium and Gliocladium].

Toxic enzymes include,

Proteases

Pseudo collagenases &

Phospho lipidases.

Trichothenes are cytotoxic and cytostatic i.e. they exhibit severe inflammatory response at lower concentrations and tissue necrosis at higher concentrations.

Gliotoxins have antibacterial, antiviral and antiphagocytic properties.

Fusarium produces several mycotoxins and destructive enzymes which cause inflammation and tissue damage. It is capable of multiplying at 37 degrees without much inflammation. Posterior chamber and lens are frequently involved causing fungal granuloma.

Fungi can penetrate Descemet's membrane with relative ease. Unlike Bacteria, fungal hyphae can be well demonstrated from anterior chamber.

Hyphal and pseudohyphal mannoproteins inhibit attachment and digestion by neutrophils. Hyphal forms are capable of invading epithelial cells and leucocytes.

Some fungi produce proteases and lipases which help host invasion and surface proteins for epithelial adherence.

IMMUNE RESPONSE

Once fungal filaments gain entry into cornea, cell mediated immunity comes into play. Polymorphonuclear neutrophils first attach themselves to hyphae through complement independent mechanisms. They produce myeloperoxidases and hydrogen peroxide which help in destruction of fungal elements.[Diamond ,Krzesicki & Wellington; Damage to pseudohyphal forms of C.albicans by neutrophils in the absence of serum. J.clin.invest.61:349;1978]

Monocytes and T-cells also exhibit such fungicidal activity. Patients with keratomycosis also demonstrate a fall in Ig M and a raise in Ig G. [serum immunoglobulins in mycotic keratitis--an interim report. Srinivasan et.al. Indian Journal of ophthalmology 1987].

HISTOPATHOLOGY

Involved cornea exhibits necrosis of lamella and acute inflammatory reaction. Antigenic response to fungal antigen results in the formation of immune ring. Severe uveitis and anterior chamber reaction occur.

Multiple microabscesses surrounding the main lesion form satellite lesions with intervening clear cornea in between.

There is severe limbal infiltration with lymphocytes and plasma cells with progressive keratitis resulting in a ring abscess.

With time hyphae can penetrate stromal lamellae and Descemet's, spreading into the anterior chamber forming retro corneal or anterior chamber inflammatory mass.

CLINICAL FEATURES

Patients usually present with a history of some form of trivial injury, often with vegetative matter.

Symptoms include photophobia, watering, redness, diminution of vision and dull pain.

Virulent fungal infections can occur in apparently normal cornea with no demonstrable deficiency in host resistance.

Less virulent organisms like candida are more common in compromised hosts like Sjogren's syndrome, erythema multiforme, endocrinopathy, immunodeficiency, alcoholism, diabetes or hypovitaminosis A.

Predisposing factors:

These include,

Lid abnormalities like, ectropion, entropion,

trichiasis,

Stye & Molluscum

Chronic dacryocystitis

Any persistent epithelial defect

Stromal ulceration

Herpes simplex infection

Topical steroid use

Contact lens wear.

Saprophytic fungi contribute to a significant number of corneal ulcers.

Upto 7% of normal eyes harbour Saprophytic fungi in lids and conjunctiva as transient inhabitants.

Most common species are,

Candida

Pencillium

Rhodotorula

Cladosporium &

Alternaria

These Saprophytic fungi become pathogenic whenever the host is predisposed.

Clinical features of keratitis caused by moulds:

Occurs more frequently in young individuals who are actively engaged in outdoor activities. Signs may be delayed for 24-48 hours after the injury.

There is no predisposing factor. Inflammation shows grayish white infiltration with rough textured surface areas raised above uninvolved cornea. Epithelial defect may or may not be present.

Stromal abscess with intact overlying epithelium is not an uncommon finding. Edges are feathery and characteristic satellite lesions are present.

Hypopyon and endothelial plaque are quite common.Antibody reaction to the fungal antigen results in a ring infiltrate –the immune ring.

Circumcorneal congestion and severe anterior chamber reaction do occur. Hypopyon is fixed which does not change position with head movements. This is due to anterior chamber invasion by fungal hyphae as well as fibrinous nature of the exudates. Another characteristic feature of fungal hypopyon is its waxing and waning nature.

Clinical features of keratitis caused by yeasts:

In general the host is compromised. Prior steroid treatment or a predisposed cornea carries a high risk.

Inflammation is more focal and suppurative resembling bacterial keratitis. Lesions are oval, plaque like elevated and widely surrounded by stromal oedema.

DIAGNOSTIC PROCEDURES

Initial procedure is collection of swabs from conjunctival sacs and lid margins using cotton swabs dipped in Brain Heart infusion broth or Trypticase Broth. These are inoculated separately on Blood agar, Thioglycollate Broth and Sabouraud's Dextrose agar.

Corneal scrapings are obtained with Kimura platinum spatula or B.P blade 15, after applying 0.5% proparacaine using slit lamp. 'C' shaped inoculations are made on the surface of culture media.

10% Potassium hydroxide mount:

For KOH mount, smear is transferred to a pre cleaned slide marked with wax pencil on the reverse.

Two drops of 10% KOH with 0.1% glycerol is placed over the smear and covered with a cover slip.

KOH dissolves cells and debris and fungal elements are highlighted.

Gram's and Giemsa stain:

Gram's stain selectively stains fungal protoplasm without staining the cell wall. Invariably fungi show a gram positive reactivity.

In Giemsa stain fungal filaments appear purple-blue.

Gracott Gomori methenamine silver staining:

Gomori methenamine silver stain stains cell walls and septa black which are easily recognized against the light green background. Principle is reduction of silver by the oxidized carbohydrate components of the fungal cell wall which stains it black.

Forester et al,described a technique by which smears stained previously by Gram's or Giemsa can be stained with this method.

PAS reagent:

PAS can demonstrate fungi in tissues and cytologic preparations. PAS hydrolyses and oxidizes cell wall polysaccharides and stains hyphae bright red.

Lactophenol cotton blue:

Lactophenol cotton blue stain clearly demonstrates fungal elements from cultures.

Calcofluor stain:

For laboratory diagnosis of mycotic keratitis, demonstration of fungal pathogens on direct microscopy and their isolation by culture is essential. The addition of Calcofluor white stain to the diagnostic armamentarium has significantly increased the sensitivity of smear examination on direct microscopy.

Acridine orange technique:

It causes a brilliant orange yellow fluorescence of fungal elements under a fluorescent microscope.

RECENT TECHNIQUES IN DIAGNOSIS

Fungal filaments from corneal scrapings can be stained with fluorescein conjugated concanavalin A. Non fluorescent stains like calcofluor white, blankophor, uvitex 2B are used with increasing success in identifying mycotic infections.

Tagged antibodies in immunoassays are also useful for picking up fungal filaments.Enzyme immunoassays and immunofluorescence are highly sensitive and specific diagnostic tools.

Use of PCR targeting of internal transcribed spacer regions and single-stranded conformation polymorphism analysis of sequence variation in different regions of rRNA genes in fungi for rapid diagnosis of mycotic keratitis is coming up.

The increased incidence of fungal infections in the recent past has been attributed to the increase in the number of human immunodeficiency virus-positive and AIDS patients. Early diagnosis of mycoses in patients is crucial for prompt antifungal therapy.

Immunological methods of diagnosis have not been found to be satisfactory, and recent research has been diverted to the use of PCR for the sensitive and early diagnosis at the molecular level. Different regions of the rRNA gene are targeted to diagnose cases of mycotic keratitis and identify the causal agents.

Six fungus-specific primers (primers ITS1, ITS2, ITS3, ITS4, invSR1R, and LR12R) are used, and the amplified products are analyzed by single-stranded conformation polymorphism (SSCP) analysis. Dendrograms of these SSCP patterns, prepared on the basis of Jaccard's coefficient, indicate that the PCR products obtained with primer pair ITS1 and ITS2 are the best for the identification of fungi.

These results are confirmed by sequencing of the PCR products, and the approach has been successfully tested experimentally for the detection of mycotic keratitis caused by Aspergillus fumigatus and is used for the diagnosis of fungal corneal ulcers in patients.

[Kumar M, Shukla PK, et.al.J Clin Microbiol. 2005 Feb;43(2):662-8.]

Corneal topography is also used extensively now a days to assess the change in corneal curvature once the keratitis has healed.

MANAGEMENT OF KERATOMYCOSIS

HISTORY:

Before 1969 most cases were treated with topical Amphotericin B with which toxicity was a major issue.

During the 1970's the related polyene Natamycin was used investigationally and became the treatment of choice for fungal keratitis.[Forster,R.K & rebel.G,The diagnosis and management of keratomycosis, Medical & surgical management. Arch.ophthal. 93. 1134,1975]

Since then so many molecules have evolved and stood the test of time like, imidazoles, triazoles and pyrimidines.

In 1979 Natamycin got FDA approval and the commercial version was put in market by Alcon as a 5% suspension.

In 1986 O'Day and associates established that the corneal uptake and penetration of C-labeled 5% Natamycin was better than 0.15% amphotericin B in corneas with intact epithelium.

Hofling & Forster worked on the comparative study of corneal penetration of six antimycotics in a in- vitro perfusion chamber using human eye.

It was found that flucytosine penetrates the best, followed by polyenes and azoles.

Pharmacotherapy of fungal eye infections:

Fungal eye infections are rare. Trauma associated with contamination by vegetative material, contact lens wear and long term corticosteroid use are common risk factors.

The aims of treatment are to preserve visual function, which depends on the rapid diagnosis and efficient administration of appropriate antifungal therapy.

This necessitates a clinical suspicion of fungal aetiology and taking appropriate smears and cultures as early as possible to identify the fungal organism. Currently there are three main classes of drugs available for use in fungal eye infections: Polyenes, Azoles as derivatives of imidazoles, and 5-Fluorocytosine.

Of the polyenes, amphotericin B, natamycin and nystatin are of clinical ophthalmic use. Based on better pharmacokinetic profiles and spectra of antifungal activity, the triazoles are the agents of choice.

Successful treatment of fungal keratitis depends on early initiation of specific therapy consisting of topically-applied antifungal agents since topical administration is most likely to provide the best opportunity for achieving therapeutic corneal levels.

Hence, the molecular weight of the various antifungal agents is of importance since it influences their ability to penetrate the corneal epithelium.

Systemic administration may be necessary for resistant fungal ulcers. for fungal endophthalmitis, to preserve visual function and eliminate the fungal pathogen, topical, systemic and possibly intraocular antifungal therapy is used, although some do not recommend use of systemic agents for exogenous endophthalmitis.

Mechanism of action of antifungals:

Large polyenes approximate the length of membrane phospholipids and form circular channels for the free passage of potassium chloride and other ions, which leads to electrolyte imbalance and eventual cell death.

Smaller polyenes accumulate on the membrane forming blisters that disrupt and cause the sterol phospholipids film to break down.

Azoles exert their antifungal effect by interference with cell membrane ergosterol synthesis, and by directly acting on the fungal cell membrane making them leaky.

In vitro MICs demonstrate that polyenes are drugs of choice for filamentous fungi and yeasts.

Triazoles are effective in treatment of Candida albicans keratitis and are as effective as amphotericin B and less toxic.

[Brooks,J.G, et al. Comparative topical triazole therapy of experimental C.albicans kertitis.Invest.oph.1990].

Azoles though useful in selective occasions like paecilomyces species, have little penetrating ability and are reserved for superficial keratitis.

Fluconazole is promising because of its penetration and distribution in ocular tissues after oral administration.

Mode of delivery:

Apart from topical drops, topical delivery of antifungals by iontophoresis and delivery by collagen shields are being developed which increases convenience and compliance.

Minimal Inhibitory Concentration for common fungi:

Organism	Amphotericin B	Natamycin	Miconazole	Ketoconazole	Flucytosine
Fusarium	1.25	2.5	12.5	25.0	>100
Aspergillus	2.5	5.0	1.6	6.25	>100
Paecilomyces	5.0	>10.0	1.6	1.6	>100
Curvularia	0.32	1.25	3.13	3.13	>100
Candida	5.0	5.0	3.13	3.13	0.39

In vitro susceptibility tests of ocular fungal isolates to antimycotics is used to rationalize treatment once organism is identified.

Studies also demonstrate that polyenes are the antimycotics of choice for filamentous fungi.

Topical corticosteroids affect all antifungals except Amphotericin B in a concentration of 0.15-0.50% .[O'Day D.M et al.Efficacy of antifungals in cornea & influence of corticosteroids Invest.ophthal. Vis.Sci. 25:331, 1984].

CLASSIFICATION OF ANTIFUNGALS

1.Polyenes

Large	small
Amphotericin B	Natamycin
Nystatin	

2.Azoles

Imidazoles	Triazoles
Miconazole	Fluconazole
Econazole	Itraconazole
Ketaconazole	Terconazole
Clotrimazole	Saperconazole
Thiabendazole	

3.Pyrimidines

Flucytosine

4.Miscellaneous

Endomycin
Hamycin
Trichomycin
Dermostatin
Lucimycin
Candicidin

AMPHOTERICIN B:

Amphotericin B is a heptaene polyene and is fungistatic,insoluble and toxic due to sterol binding in human cell membranes.

Mechanism of action:

Binds to ergosterol in cell membranes forming trans membrane channels leading onto electrolyte loss and cell death.

Spectrum of activity:

Active against candida,Aspergillus,Cryptococcus and Fusarium.

Adverse effects:

Topical : Burning, chemosis, epithelial clouding, greenish discoloration and punctuate keratopathy. Most of these are secondary to the bile salts used in drops to stabilize the solution.

Systemic toxicity : This is due to membrane damage to RBCs and renal tubular cells.

Limitations:

Toxicity, insoluble and fungistatic,cannot penetrate intact epithelium and unstable compound.

Dosage :

Topical application of 0.05-0.15% eye drops every 5 minutes for 1 hour followed by hourly application. Amphotericin B should be prepared in distilled water.

Collagen shields soaked in Amphotericin B are as effective as eye drops. Subconjunctival injections are contraindicated for fear of local necrosis.

NATAMYCIN:

This is a tetraene polyene antifungal and is the only antifungal available for commercial use.

Mechanism of action:

It accumulates by binding to sterols in cell membranes and disrupts their integrity.

Spectrum of activity:

Highly effective against filamentous fungi like Fusarium, Aspergillus, curvularia and Cladosporium.

Also active against yeast especially Candida albicans and Torulopsis. [Forster,R.K Rebell,G.The diagnosis and management of keratomycosis. Arch.ophthalmol.1975].

Dosage:

5% suspension is applied every 30 minutes for the first 3-4 days, then six to eight times daily.

Adverse effects:

Epithelial toxicity and conjunctival granuloma.

NYSTATIN:

Nystatin too is a polyene antibiotic. A solution prepared in a concentration of 50,000-1,00,000 IU/ml can be used in the treatment of superficial Candida keratitis. Usually it is administered every 2 hours.

IMIDAZOLES:

Mechanism of action:

Imidazoles inhibit ergosterol synthesis which is an important constituent of fungal cell membrane. At higher concentrations it directly causes cell wall damage. i.e. they are fungistatic at lower concentrations and fungicidal at higher concentrations in vitro.

MICONAZOLE:

Spectrum of activity:

Active against Aspergillus, Paecilomyces, Curvularia, Cladosporium and Penicillium.

Routes of administration:

Topical,subconjunctival and systemic.

Dosage :

Topical: 1% solution hourly

Subconjunctival: 5-10 mg

Systemic: 30mg/kg/day intravenously

Adverse effects:

Superficial punctuate keratitis

CLOTRIMAZOLE:

Spectrum of activity:

Highly active against Aspergillus,candida and Torulopsis.Most valuable in the treatment of keratitis caused by Aspergillus species.

Dosage:

Topical: 1% drops hourly.

Subconjunctival: 5-10 mg

KETACONAZOLE:

It is more water soluble and better absorbed after oral administration

Spectrum of activity:

Paecilomyces, Curvularia, candida and Fusarium.

Topical penetration is good and preparations are well tolerated.

Dosage:

Topical: 1%-2% hourly

Systemic: 200-400 mg/day in a single dose.

Terfendine and astemizole are contraindicated in patients taking ketaconazole.

FLUCYTOSINE:

This is a fluorinated pyrimidine and is fungistatic.

Mechanism of action:

Flucytosine is selectively taken by susceptible fungi and deaminated to fluorouracil which blocks thymidine synthesis.

Spectrum of activity:

Active against Candida,Cryptocccus and certain strains of Aspergillus, Cladosporium and Penicillium.

Flucytosine is often used along with Amphotericin B as a combination treatment in systemic Candidiasis and prevents development of resistance.

Dosage:

Topical: 1% solution hourly

Systemic:150 mg/kg/day in 4 divided doses.

Side effects:

GI upset, skin rashes, bone marrow and liver toxicity.

ITRACONAZOLE:

Newer triazole with improved spectrum against filamentous fungi.It is less effective against Fusarium.It is orally effective and is available for both oral and topical use.

Side effects include, GI upset, skin rashes, headache and reversible hepatitis.

Co administration of Terfenadine and Astemizole should be avoided.

HYPEROSMOTIC AGENTS

Topical hyperosmotic agents are useful in dehydrating oedematous corneas.

The clinical objective of topical osmotherapy is to increase the tonicity of tear film, thereby enhancing the rate of movement of fluid from cornea.

These hyperosmotic agents are hyperosmolar to ocular fluids and when applied draw fluid from cornea to the more highly osmotic tear film which is then eliminated through normal tear flow mechanisms.

Topical Sodium chloride solution [Hypersol]:

Sodium chloride is a component of all body fluids, including tears. A solution of 0.9 % is isotonic with tears.

Concentrations ranging from 2% - 10% have been tried in various studies to reduce corneal oedema.5% ointment was found to be very effective in one study[Luxenburg MN, Green K. Reduction in corneal oedema with topical hypertonic agents. American Journal of ophthalmology 1971;71;847 - 853].

Clinical use:

Used in corneal oedema secondary to any cause, bullous keratopathy and post surgical conditions.

Side effects:

Stinging, burning and irritation.

Glycerin:

Used in 50 - 100% concentration. It is used for gonioscopic examination in cases of acute angle closure glaucoma, Fuch's dystrophy and bullous keratopathy.

Glucose:

Used in 30 - 50 % concentration to treat corneal oedema.

RECENT ADVANCES IN MANAGEMENT

Vasculoepithelioplasty:

Indolent fungal keratitis respond poorly to conjuctival flap and therapeutic keratoplasty especially in terms of post operative visual recovery and cosmetic appearance.

Most of these non-healing ulcers have no blood vessels around the ulcer area. Probably ischemia produced by avascularity of cornea tamper with healing mechanism.

Therefore providing blood supply to the ulcer margins, thereby providing and supplementing necessary elements for healing to the ulcer bed, like mast cells, W.B.C., fibroblasts etc would help these ulcers to heal.

A large vessel from the limbal area nearest to the ulcer margin is chosen. It is separated with a thin apron of conjuctiva of about 1mm on either side from the fornix towards the limbus.

Conjuctiva is undermined at a depth of about 1.5mm without touching and damaging the stem cells upto 2mm inside limbus and severed with a knife.

It is advanced and sutured inside the ulcer margin with two 10-0 monofilament nylon sutures. Extreme care is taken not to damage the limbal stem cells and the conjuctival vessel. Topical antibiotic and pad is applied.

[Nichols BD : conjuctival flaps. In Kraachmer, Mannis,Holland editors: cornea, vol 3 : surgery of the cornea and conjuctiva, st lious,1997 mosby & Sanitato J.J, Kelly C.G, Kaufmann H.E; surgical management of peripheral fungal keratitis, Arch. ophthmol.102:1506,1984.]

Phototherapeutic Keratectomy in treating Keratomycosis:

Using a 193-nm excimer laser, PTK can be performed to eradicate the infiltrates and facilitate antifungal therapy.

After PTK, the ablated area undergoes rapid reepithelialization. PTK complications include mild corneal haze, astigmatism, and thinning of cornea. [Lippincott Williams & Wilkins, Inc. Cornea. 24(3):262-268, April 2005 Lin, Chang-Ping MD, PhD; Chang, Chi-Wu MD; Su, Chuan-Yi MD].

Intracameral irrigation of Amphotericin B :

Of late, intracameral injection of Amphotericin B is being tried in deep keratomycosis unresponsive to conventional anti fungals.

This helps to reduce the exudative load in the anterior chamber as well as aids in targeted delivery of Amphotericin B thereby alleviating its potential systemic side effects.[Journal of the intraocular implant & refractive society of India, Jan 2005,vol.1,No.5]

Topical application of a new antifungal agent, micafungin (MCFG), in the treatment of yeast-related corneal ulcers has given promising results.

Topical 0.1% antifungal MCFG eye drops is applied every hour till epithelialization and then 5 times a day.

[Matsumoto Y, Dogru M, Goto E, Fujishima H, Tsubota K. Department of Ophthalmology, Tokyo Dental College, Chiba, Japan]

PART 2

AIM OF THE STUDY

Aim of the study is,

1.To establish topical 10 % sodium chloride solution as a useful adjunct to 5% natamycin in the management of keratomycosis;

2.To signify its role in quickening ulcer regression thereby alleviating additional therapy and major surgical interventions like therapeutic keratoplasty.

MATERIALS AND METHODS

Study was designed as a prospective randomized controlled trial on a series of 100 cases who attended Regional institute of ophthalmology and Government ophthalmic hospital with features of fungal keratitis. Patients were briefed about the study and prior consent obtained.

Randomization:

Cases were randomized into a study and control group, to experiment on one group and compare the results with the other and to weigh the outcome statistically.

Matching:

Before randomization cases were matched for ulcer size, depth of stromal involvement and presence or absence of hypopyon to achieve maximum similarity between groups and to avoid any bias creeping in.

Inclusion criteria

Smear and culture confirmed fungal ulcers

No Hypopyon or Hypopyon < 4mm

Depth of involvement not more than two thirds of corneal stroma

Ulcers within a week of onset

Vision 3/60 and above.

Exclusion criteria

Fungal ulcers with bacterial superinfection

Predisposing systemic illness

Cases who had received some treatment outside.

Preparation of 10% sodium chloride solution (hypersol):

Usual commercially available hypertonic saline comes in 5% concentration.

We thought of using hypertonic saline in a slightly higher concentration i.e. 10% for better clinical results.

Preparation:

First we steam dried Nacl powder in a hot air oven. Then 100 gms of steam dried sodium chloride was dissolved in one liter of deionised water to give a final concentration of 10%.

Resultant solution was autoclaved and the final solution dispensed in autoclaved and labeled 5 ml bottles for patient use.

Course of the study:

For all cases we first recorded an exhaustive clinical history and then patients were subjected to slit lamp biomicroscopy .

AGE DISTRIBUTION

Age	No. of cases
0 - 10	9
11 - 20	9
21 - 30	8
31 - 40	12
41 - 50	17
51 - 60	18
61 - 70	15
71 - 80	3

SEX DISTRIBUTION

Age range	Male	Female
0 - 10	3	6
11 - 20	8	1
21 - 30	5	3
31 - 40	9	3
41 - 50	16	1
51 - 60	13	5
61 - 70	11	4
71 - 80	2	1
Total	67	33

Size, shape and depth of stromal involvement of the ulcer were recorded in the case sheet. Presence or absence satellite lesions, immune ring, stromal abscess, endothelial plaque, hypopyon and anterior chamber reaction were also recorded and documented.

Cases with high clinical suspicion of fungal keratitis were then subjected to clinical investigations to confirm the fungal etiology.

We used 10% KOH mount to identify the fungal elements and Sabouraud's agar was inoculated simultaneously and maintained at room temperature for species identification. Gram's smear was set to exclude bacterial superinfection in all the cases.

Cases were then randomly categorized as either Group A [study group] or Group B [control group].

Treatment protocol and methodology:

Group A received topical 10% sodium chloride along with 5% Natamycin,while Group B received Natamycin alone and served as control.

Dosage schedule:

Group A received 10% Sodium chloride solution one drop six times per day for 6 weeks and 5% Natamycin one drop hourly for the first week, every two hours for two weeks and then six times a day till the end of the study.

Group B received only 5% Natamycin one drop hourly for the first week, every two hours for two weeks and then six times a day till the end of the study.

Both groups received 1% atropine eye drops one drop thrice daily.

FOLLOW UP

All cases were followed biweekly for six weeks using slit lamp biomicroscopy. Signs of regression and progression were carefully looked for and recorded.

REGRESSION:

Regression was defined as

- Resolution of infiltrates
- Hypopyon clearance
- Epithelial regrowth
- Resolution of stromal oedema

PROGRESSION:

Progression was defined as

- Worsening symptoms
- Advancing infiltrates
- Increase in stromal oedema
- Formation of stromal abscess
- Descematocoele formation

OUTCOME

All the 100 cases were followed for a period of six weeks biweekly. The main outcome parameters that were looked for include, signs of regression as already mentioned and mean time taken for complete regression.

Number of cases necessitating additional therapies in the form of anterior chamber wash with Amphotericin B, treatment with other antifungals like Fluconazole,0.15% Amphotericin B,in either group were also recorded.

Surgical intervention like therapeutic keratoplasty in each group was also taken into consideration.

In group A [n = 50], 42 cases started showing signs of regression at end of 2 weeks with complete resolution of infiltrates at a mean period of 3.4 weeks.

Rest of the 8 cases required some additional intervention. Out of these 2 cases underwent Amphotericin B anterior chamber wash.

Additional topical antifungals were used in 3 cases and 3 patients necessitated therapeutic keratoplasty.

In group B [n=50], 28 cases started showing signs of regression at end of 4 weeks with complete resolution of infiltrates at a mean period of 4.6 weeks.

Rest of the 22 cases required some additional intervention. Out of these 6 cases underwent Amphotericin B anterior chamber wash. Topical antifungals (topical fluconazole) were used in 8 cases and 8 patients necessitated therapeutic keratoplasty.

Among the culture isolates, Aspergillus fumigatus predominated followed by Fusarium.

CULTURE ISOLATE

Fungal species	No. of cases	Percentage
Aspergillus fumigatus	**34**	**34%**
Fusarium	**29**	**29%**
Aspergillus flavus	**19**	**19%**
Aspergillus niger	**18**	**18%**

OUTCOME- GROUP A (n=50)

	No. of cases	Percentage
Complete regression	42	84%
Therapeutic keratoplasty	3	6%
AC Wash	2	4%
Additional antifungal	3	6%

OUTCOME - GROUP B (n=50)

	No. of cases	Percentage
Complete regression	28	56%
Therapeutic keratoplasty	8	16%
AC Wash	6	12%
Additional antifungal	8	16%

STATISTICAL ANALYSIS

Results though apparent were statistically analyzed to support the clinical findings.

We used the chi-square test (χ^2) to test the significance of difference between the two groups.

Applying the chi-square test,

$$\chi^2 = \frac{\Sigma (O- E)^2}{E}$$

Where O is the observed value

E is the expected value

Here expected value $= \frac{70 \times 50}{100}$

$= 35$

$$\chi^2 = \frac{(42-35)^2}{35} + \frac{(28-35)^2}{35} + \frac{(8-15)^2}{15} + \frac{(22-15)^2}{15}$$

$$= \frac{49}{35} + \frac{49}{35} + \frac{49}{15} + \frac{49}{15}$$

$$= \frac{98}{35} + \frac{98}{15} = 2.8 + 6.53$$

$\chi^2 = 9.33$

Allowing a degree of freedom of 1, from the probability table, expected chi-square (χ^2) value is 3.84 which is very well below our value.

Applying the null hypothesis, we get a significant P value of > 0.05, statistically signifying our clinical results.

DISCUSSION

In group A, 84% of cases showed complete regression at a mean period of 3.4 weeks, 4% of cases required Amphotericin B anterior chamber wash, 6% required additional topical antifungals and another 6% necessitated therapeutic keratoplasty.

In group B, 56% of cases showed complete regression at a mean period of 4.6 weeks, 12% of cases required Amphotericin B anterior chamber wash, 16% required additional topical antifungals and another 16% necessitated therapeutic keratoplasty.

Group	Complete regression (in weeks)
A	**3.4**
B	**4.6**

Used in such high concentrations, topical 10% sodium chloride solution causes resolution of stromal oedema and better penetration of antifungals into the organisms.

We also demonstrated that used in such high concentrations, it retards growth of bacteria in cultures.

Probably this effect may be therapeutically important in preventing superadded bacterial infections in fungal ulcers.

CONCLUSION

This comparative study clearly demonstrates, that the study group receiving 10% sodium chloride solution heals faster, rate of progression is slowed down and complications are obviously less in comparison to the group receiving 5% Natamycin alone.

Also the number of therapeutic keratoplasties is significantly less compared to the control group.

Therapeutic efficacy of 10% sodium chloride solution is attributed to its anti oedema property.

Hence topical 10% sodium chloride solution can be used along with 5% Natamycin, as a cost effective adjunct in the management of fungal keratitis.

PART - 3

BIBILOGRAPHY

1. Sir Stewart Duke Elder – Diseases of outer eye - Part - 1, volume – 8, pages 385-397
2. Gilbert Smolin – The cornea – III Edition, 229 – 253.
3. Grayson's Diseases of cornea –IV Edition, 257 – 283.
4. David.J.Apple, V Edition, pages 66 – 67.
5. R.S.Rathnagar, pathology of the Eye and orbit, I Edition, page 84
6. Kaufman - The cornea, 1988, pages 217 – 271.
7. Principles and Practice of ophthalmology – Peyman, vol.I, Pages, 294 – 298.
8. External Diseases and cornea – The foundation of the American Academy of Ophthalmology, 2000 – 2001, section 8 pages 126 - 176
9. Kaufman – Companion handbook to cornea, II Edition.

10. Duane's clinical ophthalmology, Volume IV, Chapter - 21.

11. Kanski's clinical ophthalmology – V Edition – pages 104 – 105.

12. Parson's Diseases of the Eye – 19-th Edition, Page – 213.

13. Clinical ocular pharmacology, Jimmy D.Bartlett,Siret D.Jaanus IV Edition, 2001, pages 253 - 256

14. Forster, R.K Rebell, G. The diagnosis and management of keratomycoses.Arch.ophthalmol.93:975, 1975.

15. Jones, D.B. et al. Diagnosis and management of fungal keratitis.

16. R.Srinivasan, Kanungo.R, Goyal J.L, spectrum of oculomycosis in south India. Acta ophthalmol 1991.

17. Naumann, Green, Zimmerman et.al A Histopathological study of 73 cases of mycobial keratitis American journal of ophthalmology 1967.

18. Diamond, Krzesicki & Wellington; Damage to pseudohyphal forms of C.albicans by neutrophils in the absence of serum J.clin.invest.61:349; 1978.

19. Serum immunoglobulin in mycotic keratitis--an interim report. Srinivasan et.al. Indian Journal of ophthalmology.

20. Kumar M, Shukla PK, et.al.J Clin Microbiol. 2005 Feb; 43(2): 662-8.

21. Brooks, J.G, et al.Comparative topical triazole therapy of experimental C.albicans kertitis.Invest.oph.1990.

22. O'Day D.M et al.Efficacy of antifungals and influence of corticosteroids. Invest.ophthal.Vis.Sci.25:331, 1984.

23. Luxenburg MN, green K. Reduction in corneal oedema with topical hypersonic agents.American Journal of ophthalmology 1971; 71; 847 - 853.

24. Nichols BD: conjuctival flaps. In Kraachmer, Mannis,Holland editors: cornea, vol 3 : surgery of the cornea and conjuctiva, St Lious,1997 mosby & Sanitato J.J, Kelly C.G, Kaufmann surgical management of peripheral fungal keratitis, Arch.ophthmol.102:1506,1984.

25. Lippincott Williams & Wilkins, Inc. Cornea. 24(3):262-268, April 2005 Lin, Chang-Ping MD, PhD; Chang, Chi-Wu MD; Su, Chuan-Yi MD.

26. Journal of the intraocular implant & refractive society of India. Jan 2005,vol.1,No.5

27. Matsumoto Y, Dogru M, Goto E, Fujishima H, Tsubota K. Department of Ophthalmology, Tokyo Dental College, Chiba, Japan.

28. Corneal topography Principles & applications Melanie C Corbet Emanuel S Rosen, David PSO'Brart. I Edition. Page 111.

PROFORMA

Name: Date of study:

Address:

Age: Date of Admission:

Sex: Date of Discharge:

Occupation:

OP No: MRD No:

Complaints: Pain, redness, watering, photophobia . RE/LE

Duration:

History of present illness:

History of injury with stick/Thorn/Fall of dust/others

Past history: H/O T.B/leprosy/Diabetes/Syphilis

Family History:

General Examination:

OCULAR EXAMINATION: RE LE

Visual Acuity:

Lids & Adnexa:

Conjunctiva:

Cornea:

Ulcer Size/Shape:

Site: Central/Marginal

Hypopyon Size:

Satellite Lesion:

Depth of involvement:

Anterior Chamber:

Iris:

Pupil:

Lens:

Corneal sensation:

Fluorescein staining:

INVESTIGATIONS:

Duct:

Conjunctival Smear:

Corneal smear[Gram's/Giemsa]

KOH Prep:

Fungal culture

Urine-Albumin/Sugar/RBS:

THERAPEUTIC TRIAL

STUDY GROUP	CONTROL GROUP
[A]	[B]
[Topical 10% hypersol & Topical 5% Natamycin]	[Topical 5% Natamycin alone]

FOLLOW UP

Week	**1**	**2**	**3**	**4**	**5**	**6**
Ulcer Size:						
Hypopyon						
Stromal oedema						
Infiltrates						

REMARKS:

Amphotericin AC wash:

Additional antifungal (if any):

Therapeutic keratoplasty:

MASTER CHART

SN	NAME	AG	SX	IP.No	IN	US	UD	SL	HY	KOH	FC	GP	TR	TKP	AW	OA
1	kanniga	45	F	395936	+	5	1/2	+	+	SH	FU	A	_			+
2	Suresh	19	M	396396	+	3	2/3	_	+	SH	AFL	B	+			
3	Samuel	15	M	396509	+	2	2/3	_	+	SH	AFL	B	+			
4	Kumari	22	F	396340	+	4	2/3	_	+	SH	AN	B	_	+		
5	Vikram	14	M	395752	+	3	2/3	_	+	SH	AFL	B	+			
6	Pencillamma	40	F	396471	+	2	1/2	+	+	SH	FU	B	_		+	
7	Lakshmi	55	F	396166	+	3	2/3	_	_	SH	AFL	B	_	+		
8	Jamal	65	M	396587	+	3	1/2	_	+	SH	AFU	B	_		+	
9	Rajammal	50	F	396299	+	2	2/3	_	_	SH	FU	B	+			
10	Rasammal	75	F	396649	+	4	1/2	+	+	SH	AFL	B	_			+
11	Muthalamma	65	F	396480	+	3	2/3	_	+	SH	AN	A	+			
12	Joseph	11	M	396359	+	4	2/3	_	+	SH	FU	A	_	+		
13	Thirurani	58	F	394550	+	2	2/3	+	+	SH	AFU	A	+			
14	Pushparani	32	F	396722	+	3	1/2	_	_	SH	AFU	A	_			+
15	Ramasamy	50	M	396541	+	3	2/3	+	_	SH	AN	A	+			
16	Natarajan	47	M	395465	+	2	1/2	_	_	SH	FU	A	+			
17	Kasthuri	45	F	396386	+	3	2/3	_	+	SH	AFU	A	+			
18	Maran	51	M	395231	+	5	1/2	+	_	SH	AFU	A	+			
19	Pitchandi	40	M	396669	+	2	2/3	+	_	SH	FU	A	+			
20	Snekha	4	F	396529	_	2	1/2	_	_	SH	AFU	A	+			
21	Desigan	45	M	395893	+	3	1/2	_	_	SH	AFU	A	+			
22	Yasodha	55	F	395984	+	4	2/3	+	_	SH	AN	A	+			
23	Mahesh	12	M	396748	+	3	1/2	_	+	SH	FU	B	+			
24	Velu	62	M	396762	+	3	1/2	+	+	SH	AFU	B	+			
25	Palani	37	M	396725	+	3	2/3	_	_	SH	AFU	B	_	+		
26	Natarajan	47	M	396803	+	2	2/3	_	_	SH	AN	B	+			
27	Ramanathan	68	M	396775	+	3	1/2	_	+	SH	FU	B	+			
28	Muniammal	30	F	396892	+	4	1/2	_	+	SH	FU	B	+			
29	Muthu	46	M	396714	+	2	1/2	_	+	SH	AFU	B	+			
30	Venkaiah	65	M	396868	+	3	2/3	+	+	SH	AFU	B	+			
31	Devarani	50	F	396553	+	3	2/3	_	+	SH	AFL	A	+			
32	Ramadoss	47	M	396955	+	2	2/3	_	_	SH	FU	A	+			
33	Gajendran	45	M	397162	+	3	1/2	_	_	SH	AFU	A	_	+		
34	Lingammal	45	F	397117	+	2	1/2	+	_	SH	FU	A	+			
35	Sandhya	43	F	396769	+	3	2/3	_	_	SH	AN	A	+			
36	Padmavathy	45	F	397074	+	2	2/3	_	_	SH	AFU	B	+			
37	Loganathan	57	M	396923	+	3	1/2	_	+	SH	FU	B	+			
38	Munusamy	50	M	397216	+	5	1/2	_	+	SH	AN	B	+			
39	Muthu	27	M	397217	+	2	2/3	_	+	SH	AFU	B	+			
40	Manikandan	18	M	397073	+	4	2/3	_	_	SH	AN	B	+			
41	Murthy	25	M	397180	+	3	2/3	+	+	SH	FU	A	+			
42	Ayisha	53	F	397222	+	2	2/3	_	_	SH	AFU	A	+			
43	Munusamy	21	M	397201	+	3	2/3	_	+	SH	AN	A	+			
44	Ramasamy	67	M	396961	+	4	1/2	_	_	SH	AFU	A	+			
45	Shesadri	25	M	397156	+	2	1/2	_	+	SH	FU	A	+			
46	Gabriel	62	M	396799	+	3	1/2	_	_	SH	AFU	A	+			
47	Balaji	18	M	396948	+	2	1/2	_	+	SH	AFL	A	+			
48	Chellavelu	55	M	395193	+	3	2/3	+	+	SH	AFL	A	+			
49	Palpandian	58	M	396717	+	2	2/3	_	+	SH	FU	A	+			

SN	NAME	AG	SX	IP.No	IN	US	UD	SL	HY	KOH	FC	GP	TR	TKP	AW	OA
50	Palani	37	M	396930	+	2	1/2	_	+	SH	FU	B	_		+	
51	Dhandapani	51	M	397115	+	3	2/3	_	+	SH	AFU	B	_	+		
52	Duraisamy	50	M	396711	+	3	2/3	_	+	SH	AN	B	_		+	
53	Raju	56	M	396946	+	2	2/3	+	_	SH	AFU	B	_	+		
54	Visalatchi	55	F	396996	+	2	1/2	_	_	SH	AFU	B	+			
55	Rosaiah	45	M	396814	+	5	1/2	_	_	SH	AFU	B	_	+		
56	Pitchandi	40	M	396794	+	3	2/3	+	_	SH	AFL	B	+			
57	Arumugam	58	M	396903	+	2	1/2	+	+	SH	AFL	B	_			+
58	Munusamy	65	M	396852	+	2	2/3	_	_	SH	FU	B	_	+		
59	Anjammal	45	F	397099	+	3	1/2	_	+	SH	FU	B	_			+
60	Mutulashmi	60	F	397081	+	3	2/3	+	_	SH	FU	B	+			
61	Jeyasri	1	F	397469	+	3	2/3	_	+	SH	AFL	B	_		+	
62	Karupamma	70	F	397219	+	3	1/2	_	+	SH	AN	B	+			
63	Rubavalli	15	F	397046	+	2	1/2	_	+	SH	AFL	B	_			+
64	Kasinathan	46	M	397401	+	2	1/2	_	+	SH	AFL	A	+			
65	Kirthiraj	50	M	397366	+	2	2/3	+	_	SH	AN	B	+			
66	Shiva	10	M	397187	+	3	2/3	+	_	SH	AFU	A	+			
67	Shanmugam	33	M	397566	+	2	1/2	_	_	SH	AFU	A	_		+	
68	Kaliammal	68	F	397237	+	3	1/2	_	+	SH	AFU	A	_	+		
69	Akila	9	F	397620	+	2	2/3	_	+	SH	FU	A	+			
70	Anandi	9	F	397271	+	4	1/2	_	+	SH	AFL	A	+			
71	Thanganadar	65	M	397742	+	2	2/3	_	+	SH	AFU	B	+			
72	Saravanan	14	M	397244	+	3	2/3	+	+	SH	AFL	A	+			
73	Mari	80	F	397323	+	3	2/3	_	+	SH	AFU	B	+			
74	Vijayan	23	M	397390	+	2	2/3	_	+	SH	AN	B	+			
75	Rathinam	66	M	397606	+	3	2/3	+	+	SH	FU	A	+			
76	Sivakumar	20	M	397320	+	2	1/2	_	_	AF	AFU	B	+			
77	Malayan	37	M	397269	+	4	1/2	_	+	SH	AN	B	+			
78	Sundaram	47	M	397400	+	2	1/2	_	_	SH	AFL	A	+			
79	Arasu	36	M	397395	+	4	1/2	_	+	SH	FU	B	+			
80	Ganapathi	60	M	397059	+	2	1/2	_	+	SH	AFU	B	_		+	
81	Rajendran	45	M	397438	+	4	1/2	_	+	SH	AFU	A	+			
82	Rathinam	66	M	397347	+	3	2/3	_	+	SH	AFU	B	+			
83	Gabriel	62	M	397391	+	4	2/3	+	+	SH	FU	A	+			
84	Rajkumar	3	M	397480	+	2	2/3	_	+	SH	FU	B	_			+
85	Rathinam	65	M	397084	+	2	2/3	_	+	SH	AFL	A	_		+	
86	Deepika	2	F	396931	+	3	2/3	_	_	SH	AFL	A	_			+
87	Nagarajan	40	M	396921	+	2	1/2	_	+	SH	AN	A	+			
88	Durga	7	F	397421	+	3	1/2	+	_	SH	FU	B	_			+
89	Muthulakmi	50	F	397417	+	2	1/2	_	+	SH	FU	A	+			
90	Mohamed	38	M	396815	+	2	2/3	_	+	SH	AFU	B	_			+
91	Kannan	57	M	397718	+	3	2/3	+	+	SH	AFU	A	+			
92	Amirtammal	63	F	397578	+	4	1/2	_	+	SH	AFL	A	+			
93	Sanyasi	60	M	397627	+	3	1/2	_	+	SH	FU	A	+			
94	Chinaammal	40	F	397739	+	3	2/3	+	_	SH	AFU	A	+			
95	Malliga	28	F	396733	+	2	1/2	_	_	SH	AN	A	+			
96	Elumalai	57	M	397798	+	2	2/3	_	_	SH	AN	A	+			
97	krishnan	45	M	397443	+	2	1/2	_	+	SH	FU	A	+			
98	Muthu	47	M	394321	+	4	1/2	_	+	SH	AFU	B	_	+		
99	Munusamy	75	M	397629	+	2	2/3	_	+	SH	AN	A	+			
100	Ramasamy	50	M	397883	+	2	2/3	_	_	SH	FU	B	_			+

KEY TO MASTER CHART

SN	**Serial number**
AG	**Age**
SX	**Sex**
M	**Male**
F	**Female**
IP. No	**Inpatient number**
IN	**H/O Injury**
US	**Ulcer size (in mm)**
UD	**Ulcer depth (Extent of stromal involvement)**
SL	**Satellite lesions**
HY	**Hypopyon**
FC	**Fungal culture**
GP	**Group**
TR	**Total regression**
TKP	**Therapeutic keratoplasty**
AW	**Amphotericin AC wash**
OA	**Other antifungal (Fluconazole)**
SH	**Septate Hyphae**
FU	**Fusarium**
AFL	**Aspergillus flavus**

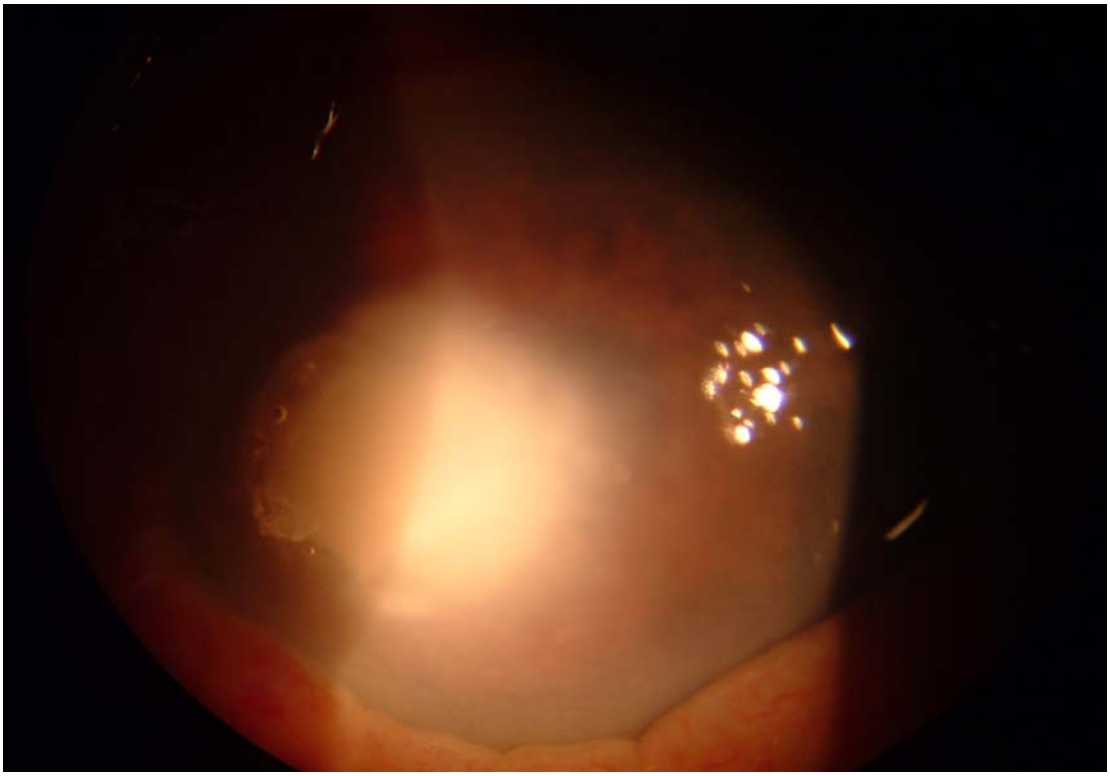
AN	**Aspergillus niger**
AFU	**Aspergillus fumigatus**
A	**Group A**
B	**Group B**

LIST OF SURGERIES

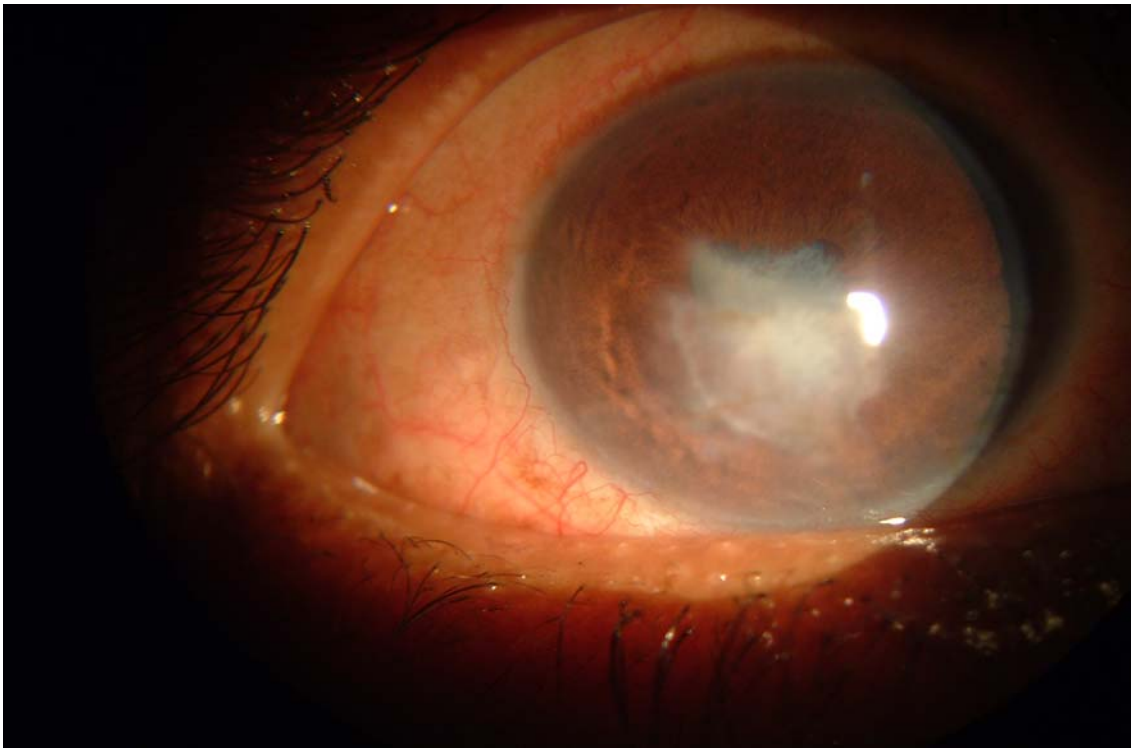
S.NO	NAME	AGE	SEX	IP.NO	DIAGNOSIS	SURGERY
1	Kumari	22	F	396340	Resistant Fungal keratitis	TKP
2	Lakshmi	55	F	396166	Resistant Fungal keratitis	TKP
3	Joseph	11	M	396359	Resistant Fungal keratitis	TKP
4	Palani	37	M	396725	Resistant Fungal keratitis	TKP
5	Gajendran	45	M	397162	Resistant Fungal keratitis	TKP
6	Dhandapani	51	M	397115	Resistant Fungal keratitis	TKP
7	Raju	56	M	396946	Resistant Fungal keratitis	TKP
8	Rosaiah	45	M	396814	Resistant Fungal keratitis	TKP
9	Munusamy	65	M	396852	Resistant Fungal keratitis	TKP
10	Kaliammal	68	F	397237	Resistant Fungal keratitis	TKP
11	Muthu	47	M	394321	Resistant Fungal keratitis	TKP

TKP - Therapeutic keratoplasty

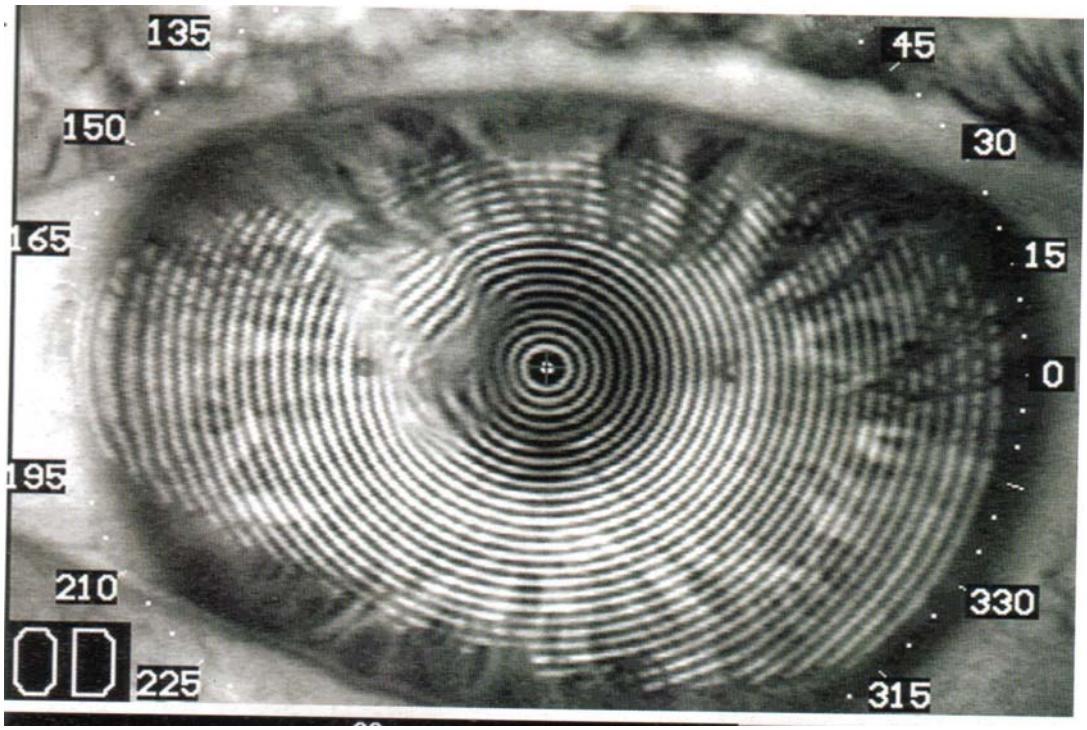
BEFORE TREATMENT

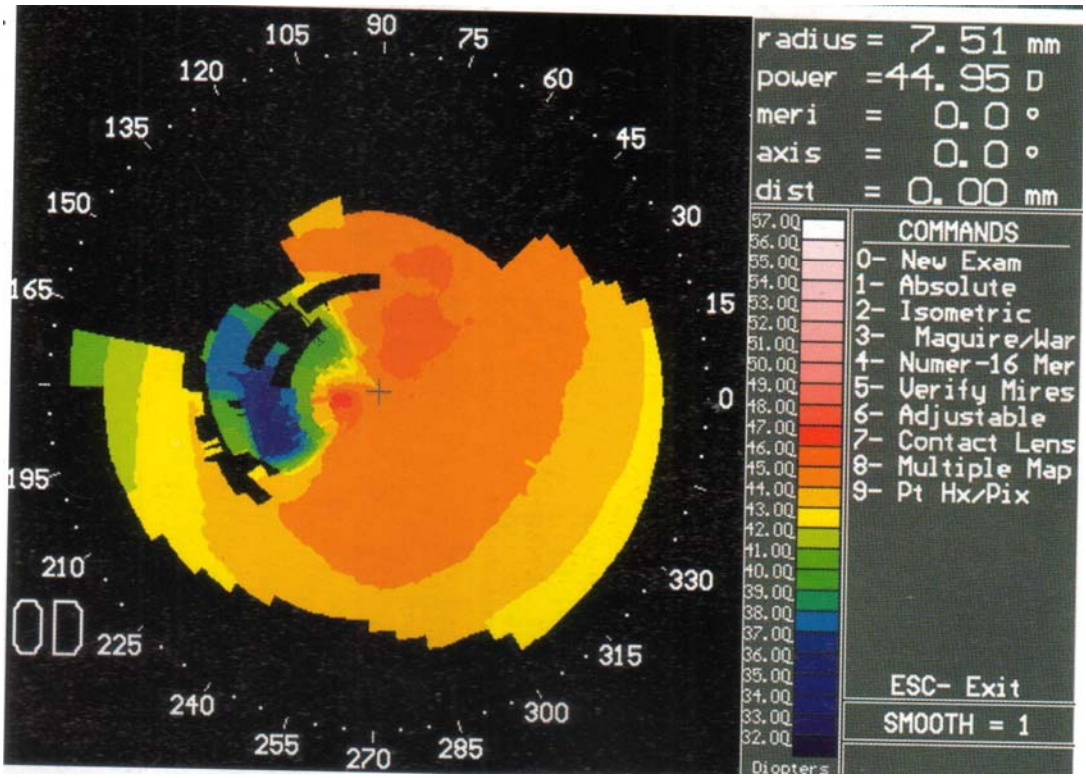


AFTER 4 WEEKS OF TREATMENT WITH 10% HYPERSOL

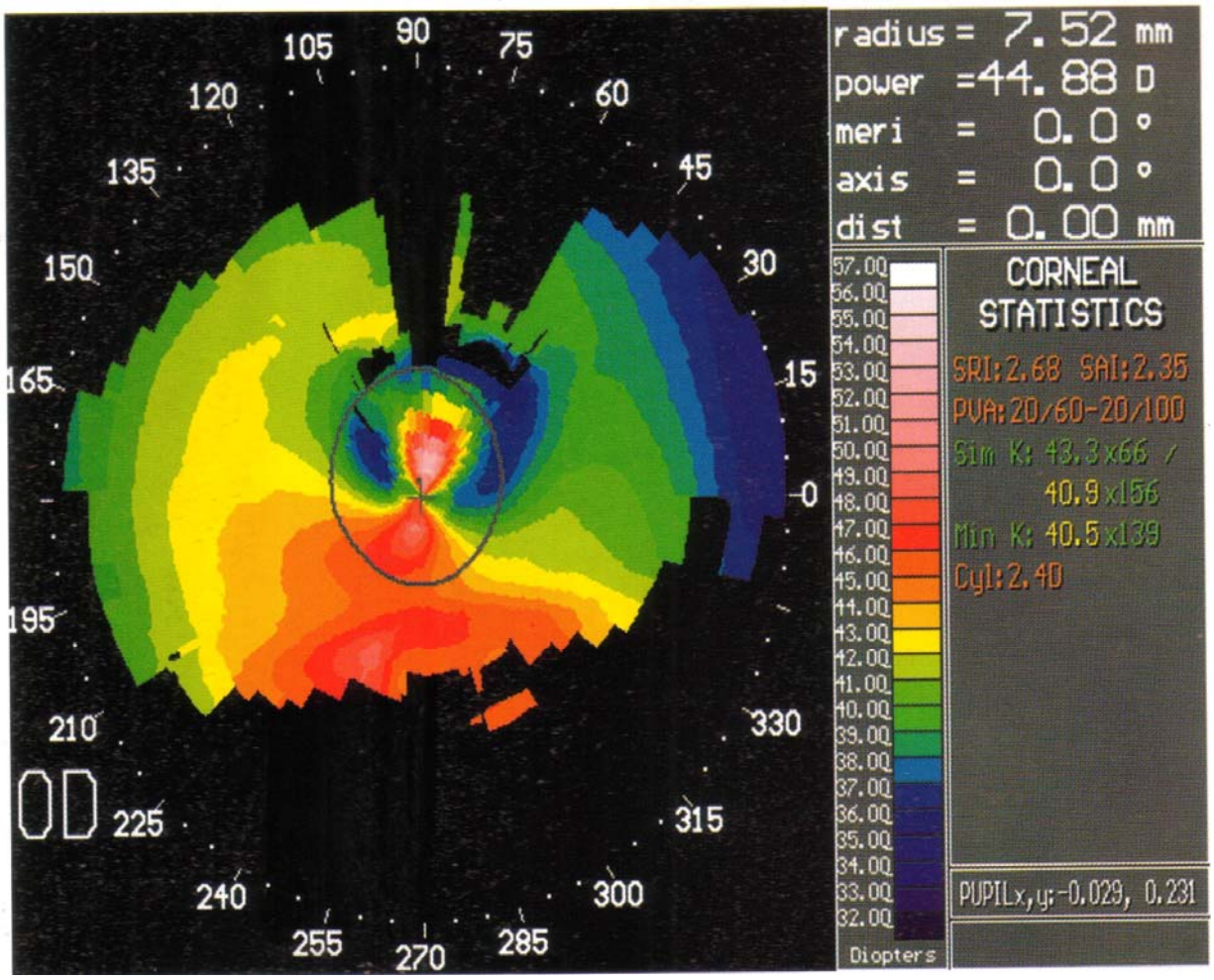


A LOCALISED DEPRESSION OF THE SUPEROTEMPORAL PARACENTRAL CORNEA IN KERATOMYCOSIS

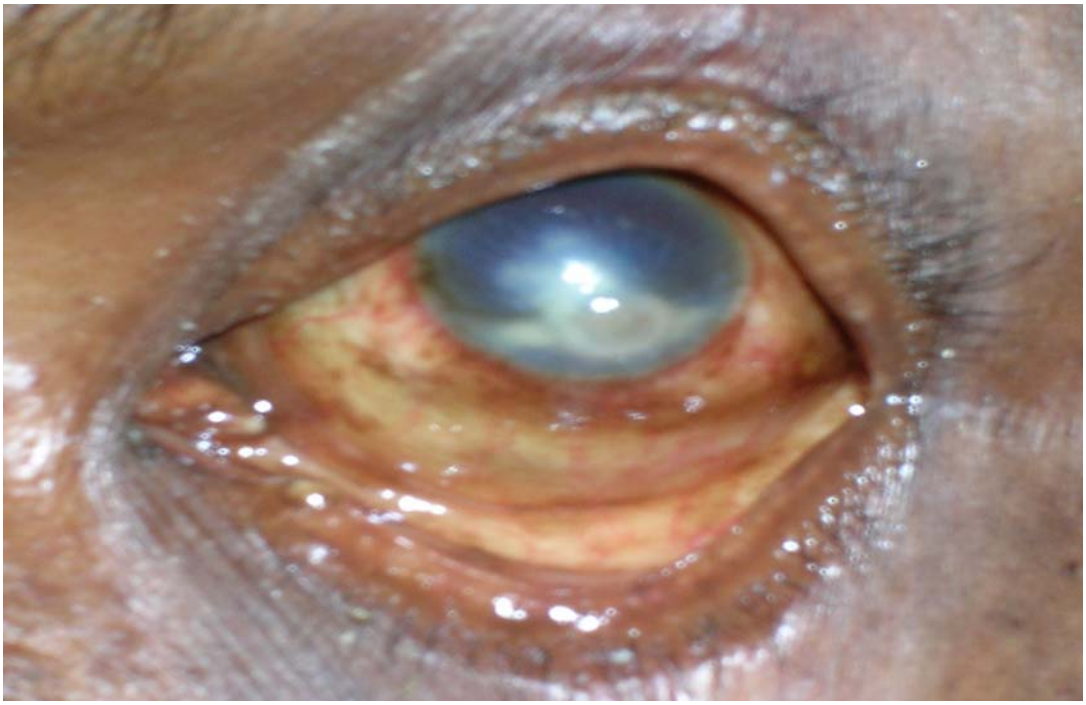




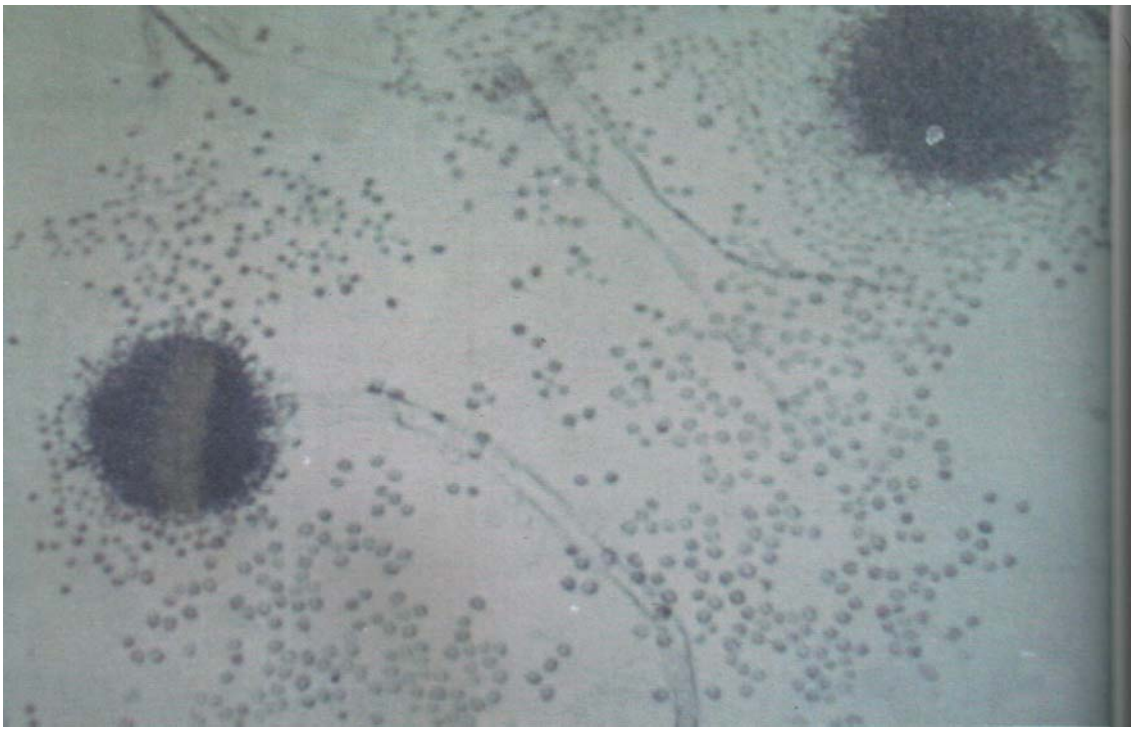
CORNEAL TOPOGRAPHY SHOWING HEALED KERATITIS CAUSING A LOCALISED DEPRESSION IN THE SUPERIOR PARACENTRAL CORNEA.



CLASSICAL FUNGAL ULCER WITH FEATHERY MARGINS



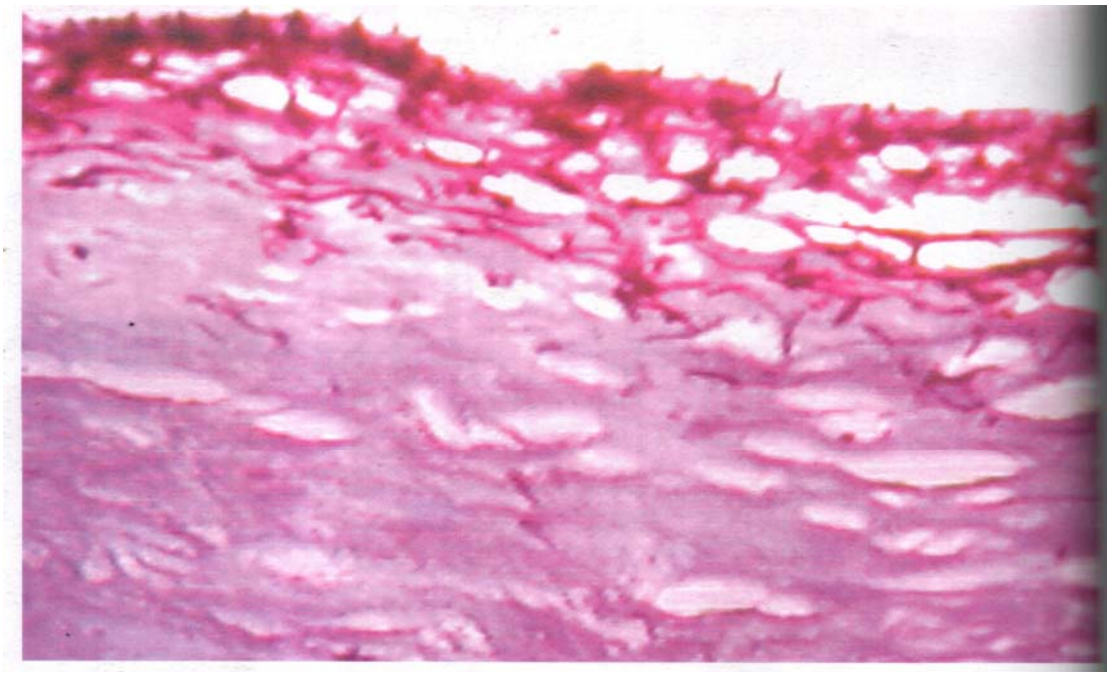
KOH MOUNT SHOWING SEPTATE HYPHAE



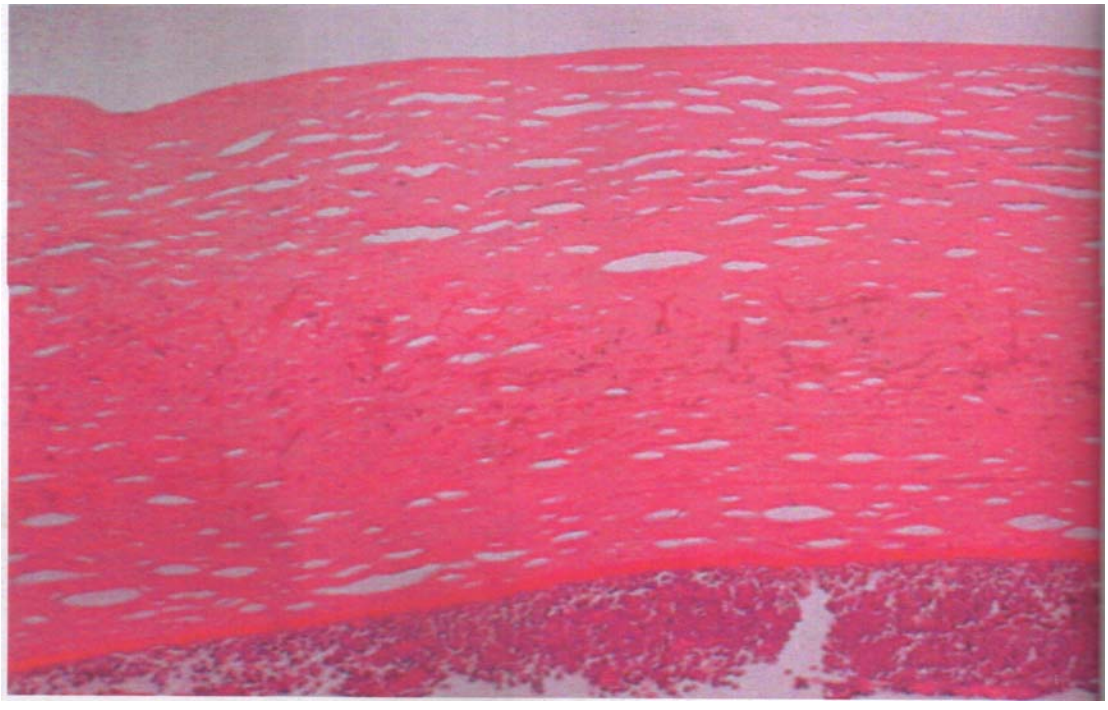
HPE SHOWING FUNGAL HYPHAE IN ANTERIOR STROMA

LACTOPHENOL COTTON BLUE STAINING SHOWING BOAT SHAPED SPORES OF FUSARIUM

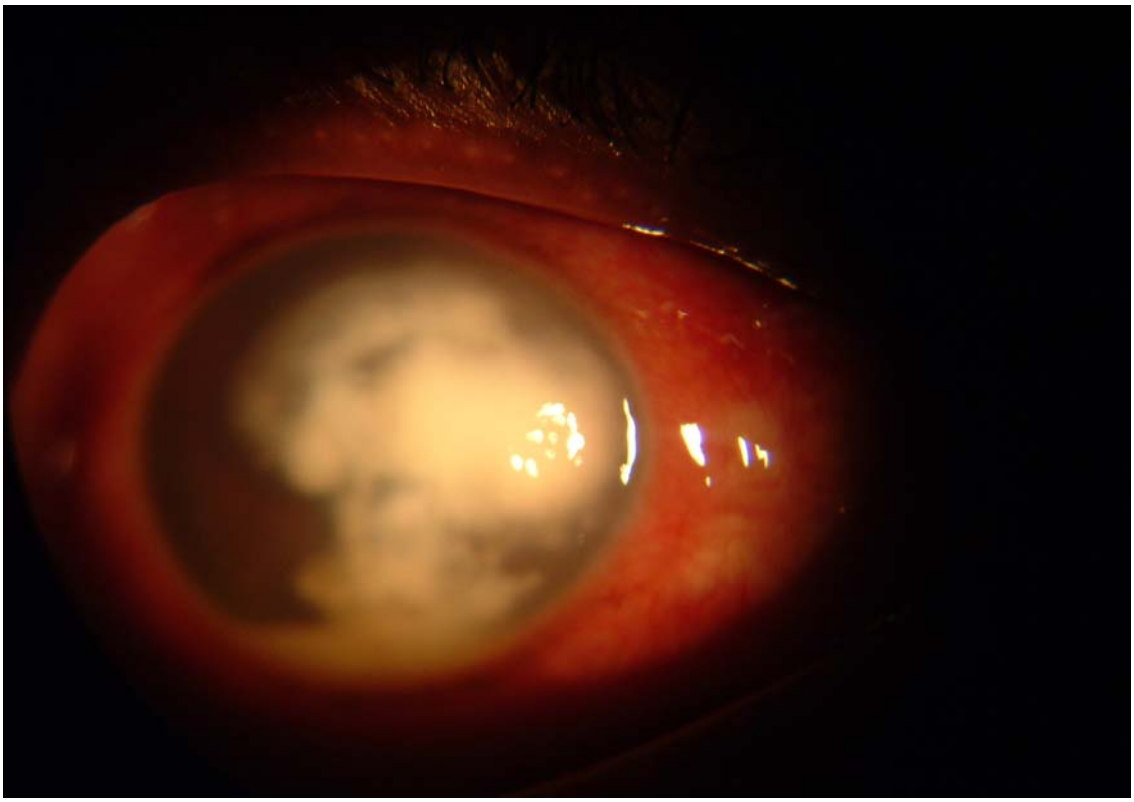
HPE - FUNGAL HYPHAE IN SUPERFICIAL STROMA



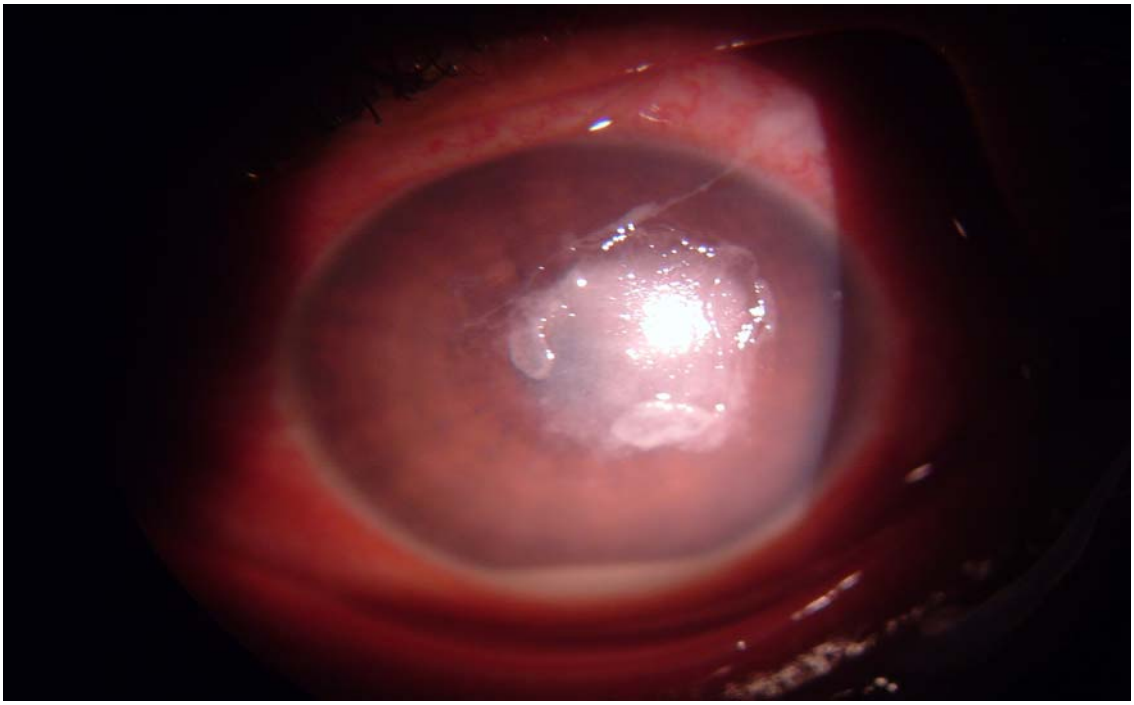
PAS STAINING SHOWING MID STROMAL HYPHAE

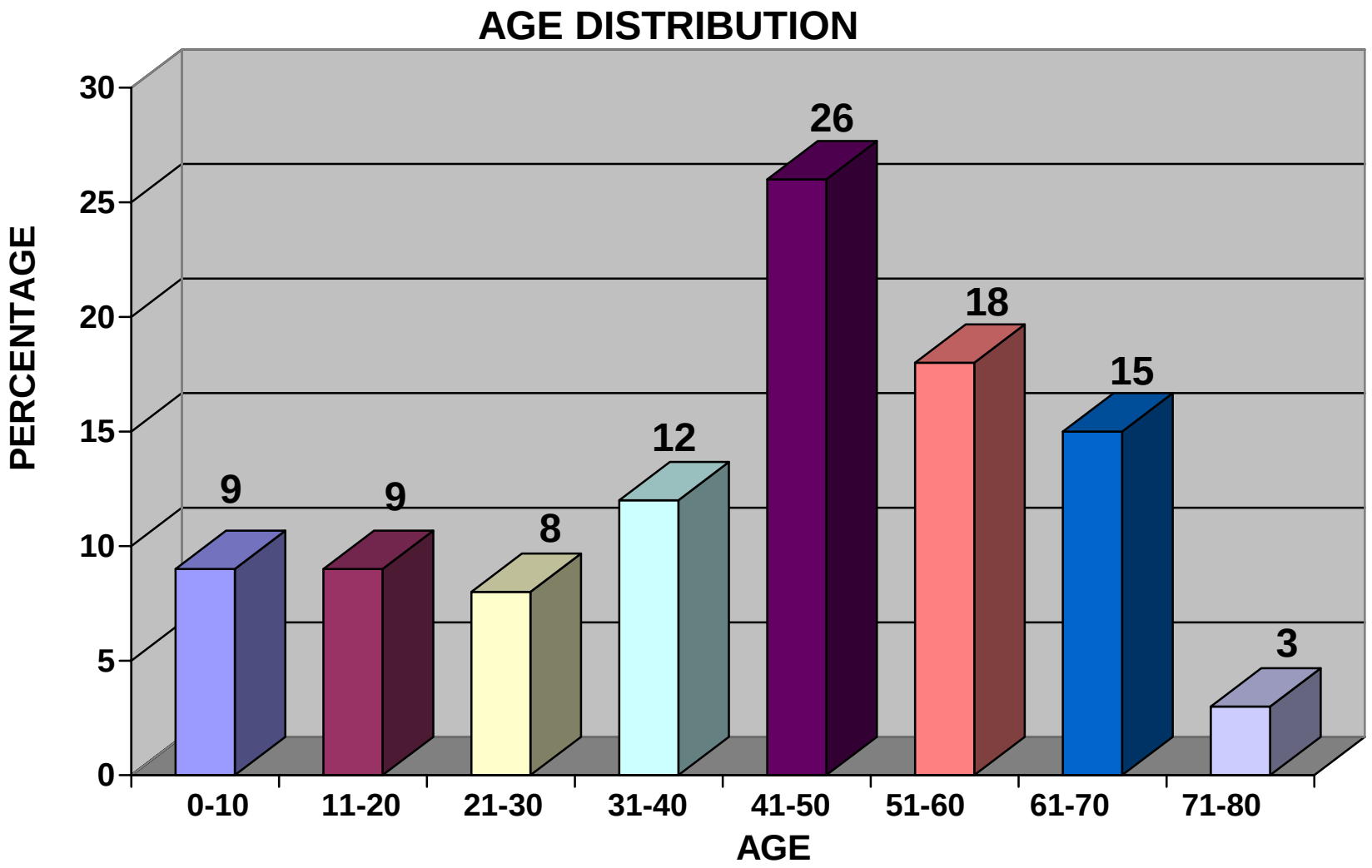


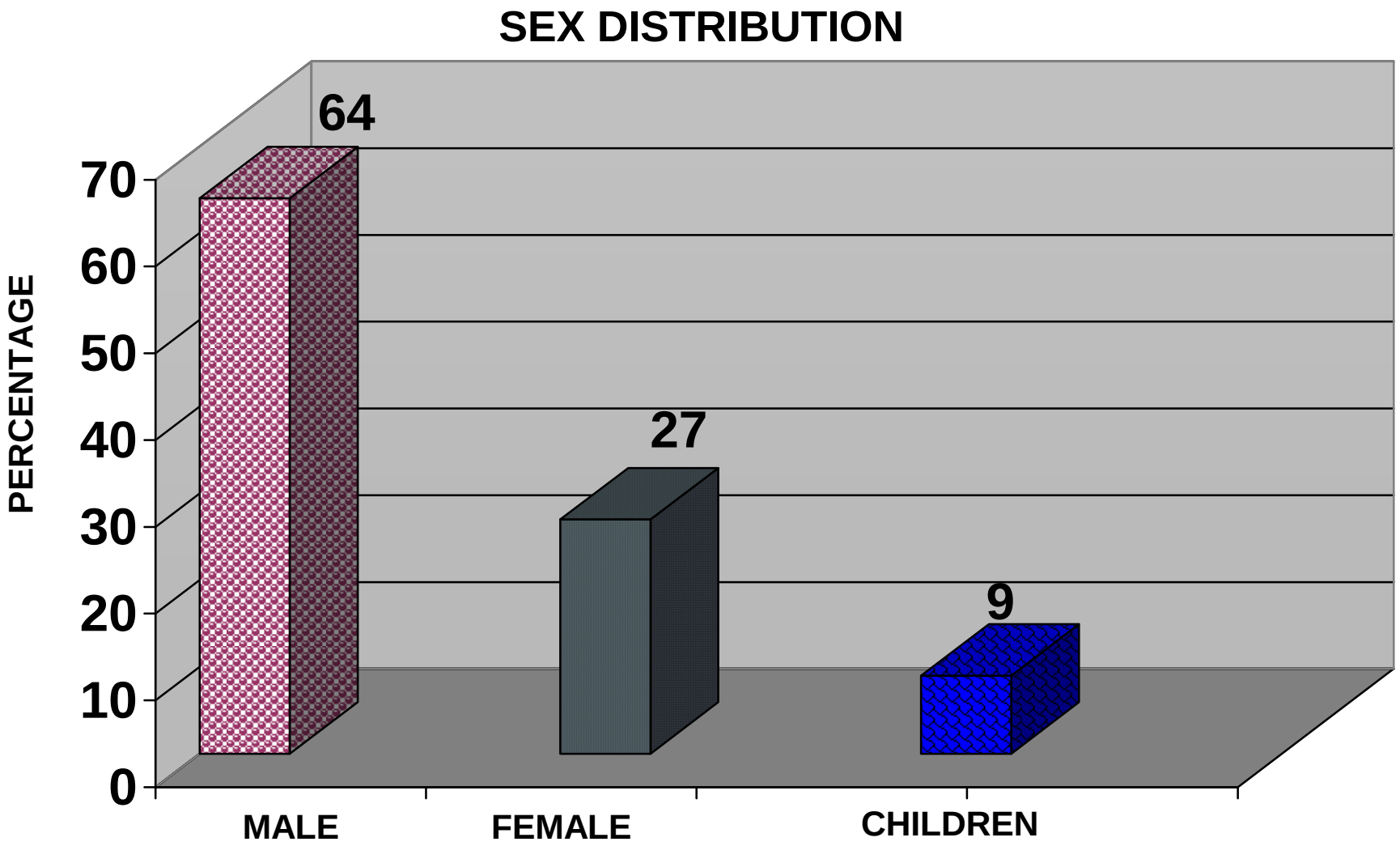
BEFORE TREATMENT



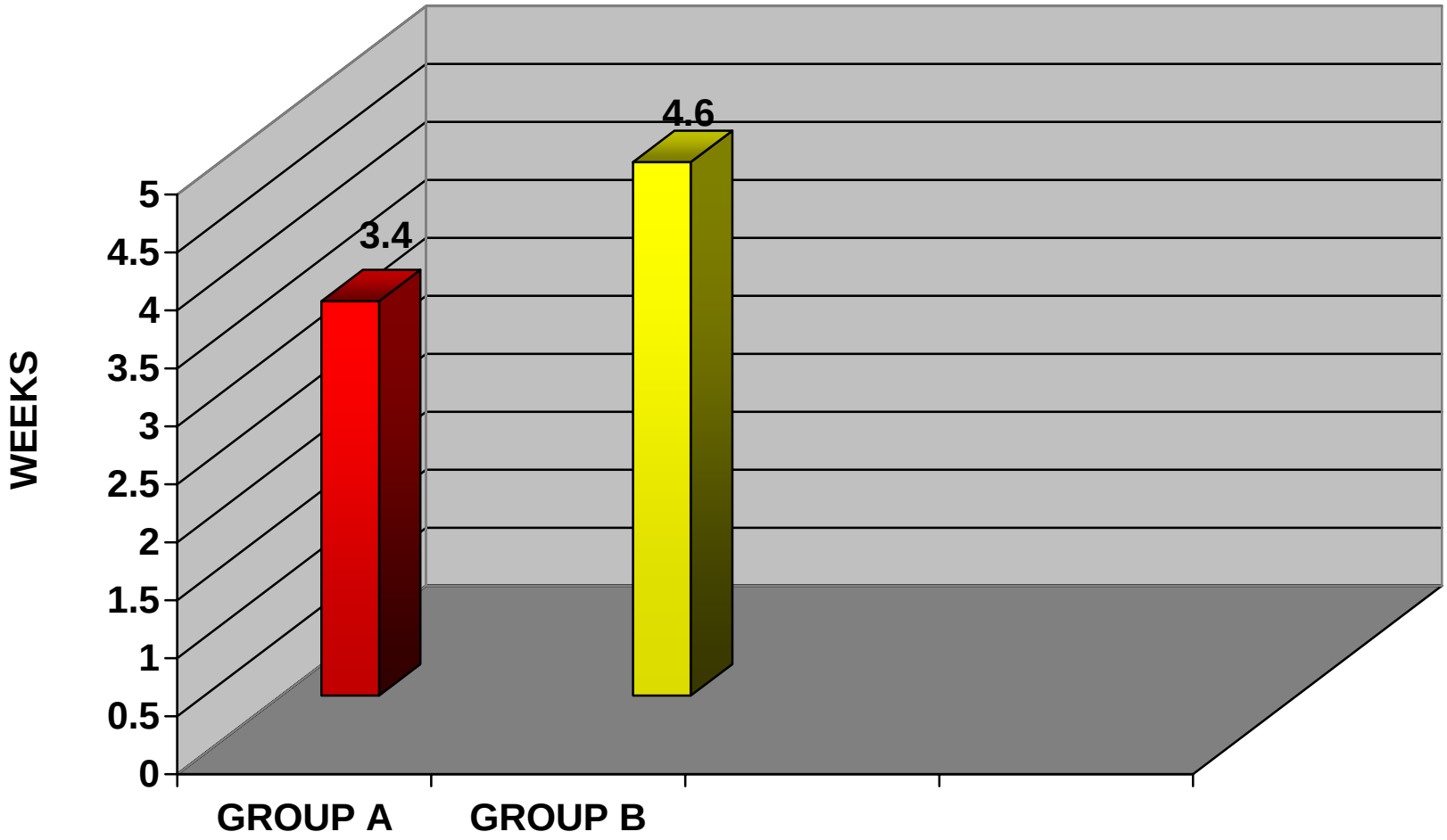
AFTER 4 WEEKS OF TREATMENT WITH 10% HYPERSOL

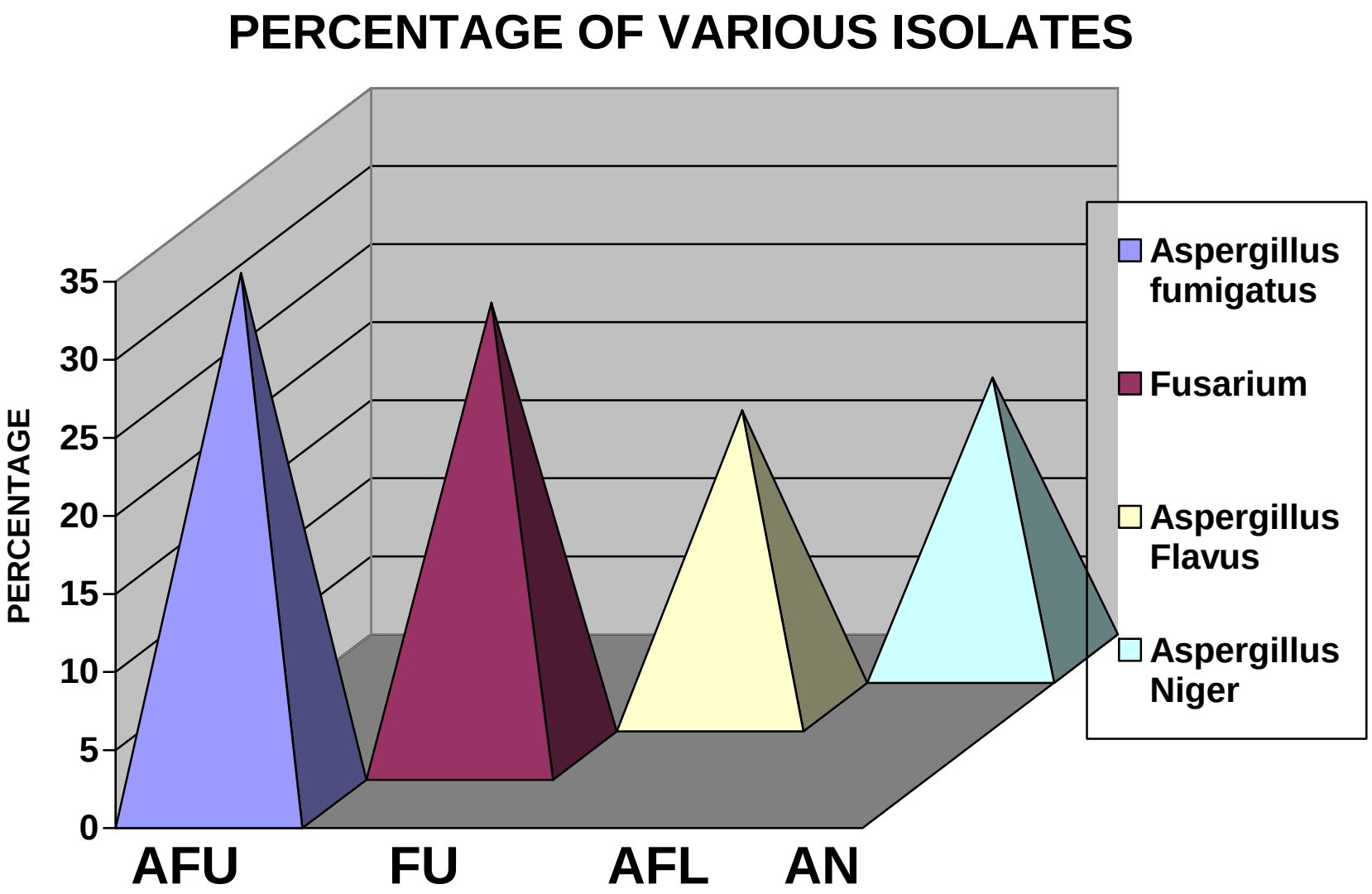


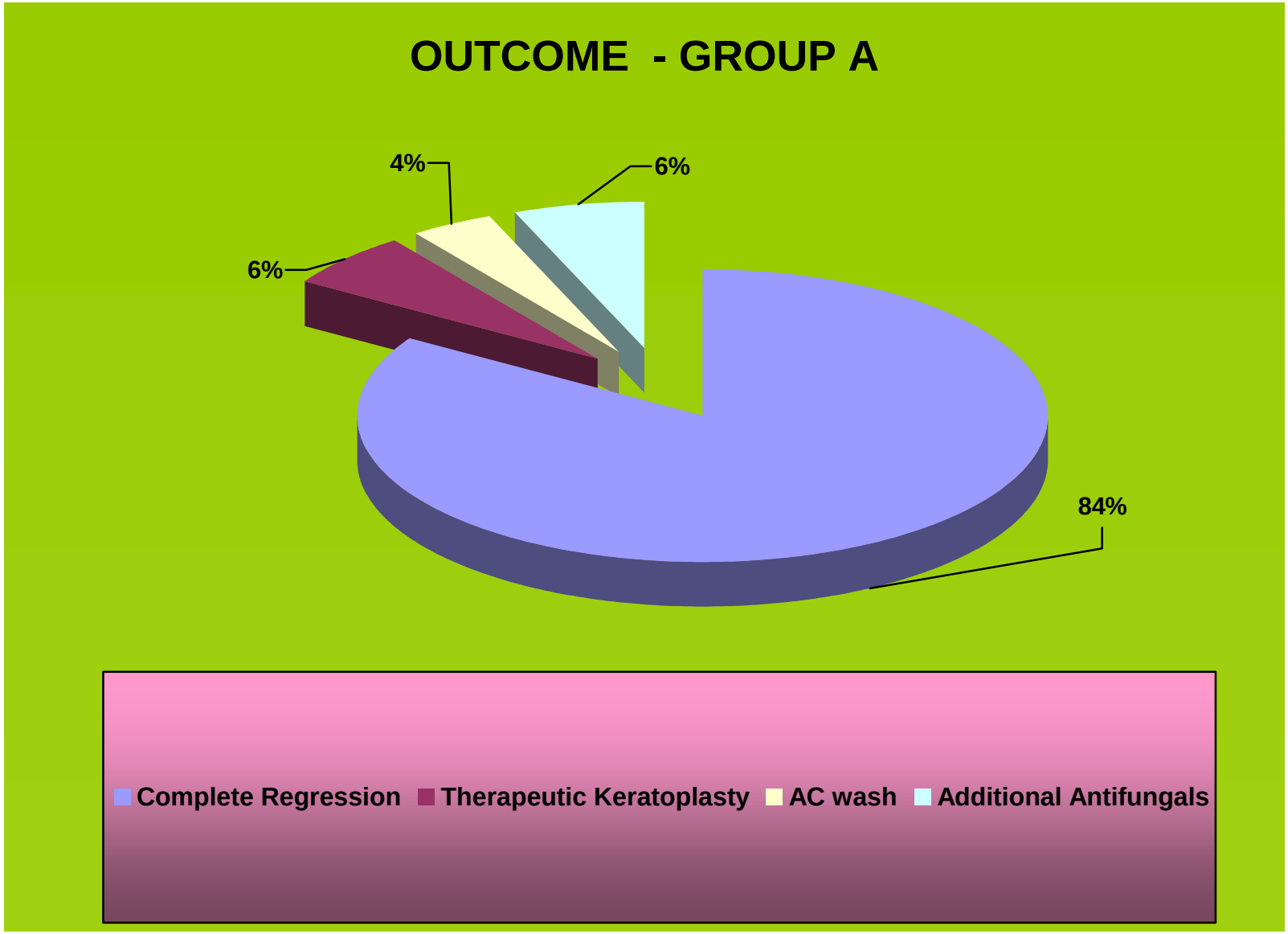

AGE DISTRIBUTION
PERCENTAGE
30
25
20
15
10
5
0
9
9
8
12
26
18
15
3
0-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
AGE

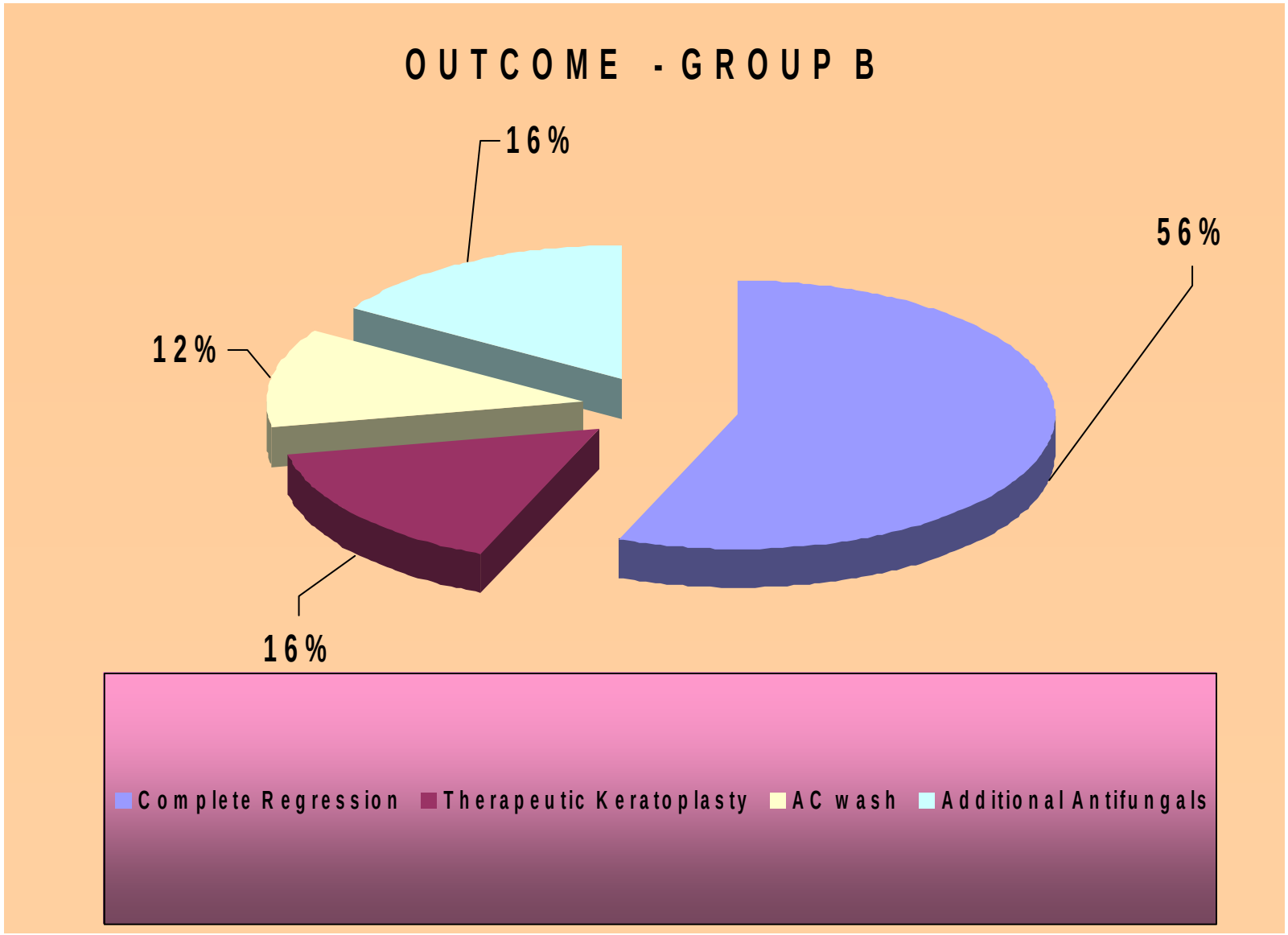

SEX DISTRIBUTION
PERCENTAGE
70
60
50
40
30
20
10
0
64
27
9
MALE
FEMALE
CHILDREN

ULCER REGRESSION RATE




PERCENTAGE OF VARIOUS ISOLATES
PERCENTAGE
35
30
25
20
15
10
5
0
AFU
FU
AFL
AN
Aspergillus fumigatus
Fusarium
Aspergillus Flavus
Aspergillus Niger


OUTCOME - GROUP A
4%
6%
6%
84%
Complete Regression
Therapeutic Keratoplasty
AC wash
Additional Antifungals


OUTCOME - GROUP B
16%
56%
12%
16%
Complete Regression
Therapeutic Keratoplasty
AC wash
Additional Antifungals